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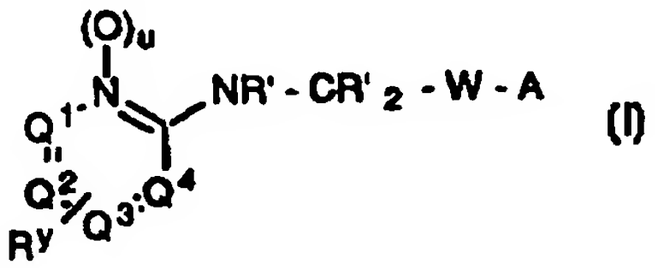
(54) Title: VITRONECTIN RECEPTOR ANTAGONISTS

(57) Abstract

Compounds of formula (I) are disclosed, wherein: A is a fibrinogen antagonist template; W is a linking moiety of the form -$(CHR^g)_a$-U-$(CHR^g)_b$-V-; $Q^1$, $Q^2$, $Q^3$ and $Q^4$ are independently N or C-$R^y$, provided that no more than one of $Q^1$, $Q^2$, $Q^3$ and $Q^4$ is N; R' is H or $C_{1-6}$alkyl, $C_{3-7}$cycloalkyl-$C_{0-6}$alkyl or Ar-$C_{0-6}$alkyl; $R^g$ is H or $C_{1-6}$alkyl, Het-$C_{0-6}$alkyl, $C_{3-7}$cycloalkyl-$C_{0-6}$alkyl or Ar-$C_{0-6}$alkyl; $R^k$ is $R^g$, -C(O)$R^g$ or -C(O)O$R^g$ $R^i$ is H, $C_{1-6}$alkyl, Het-$C_{0-6}$alkyl, $C_{3-7}$cycloalkyl-$C_{0-6}$alkyl, Ar-$C_{0-6}$alkyl, Het-$C_{0-6}$alkyl-U'-$C_{1-6}$alkyl, $C_{3-7}$cycloalkyl-$C_{0-6}$alkyl-U'-$C_{1-6}$alkyl or Ar-$C_{0-6}$alkyl-U'-$C_{1-6}$alkyl; $R^y$ is H, halo, -O$R^g$, -S$R^g$, -CN, -N$R^g R^k$, -$NO_2$, -$CF_3$, $CF_3S(O)_r$-, -$CO_2R^g$, -COR$^g$ or -CON$R^g_2$, or $C_{1-6}$alkyl optionally substituted by halo, -O$R^g$, -S$R^g$, -CN, -N$R^g$R'', -$NO_2$, -$CF_3$, R'$S(O)_3$-, -$CO_2R^g$, -COR$^g$ or -CON$R^g_2$; U and V are absent or CO, $CR^g_2$, C(=$CR^g_2$), $S(O)_c$, O, N$R^g$, C$R^g$O$R^g$, C$R^g$(O$R^k$)C$R^g_2$, $CR^g_2CR^g(OR^k)$, C(O)$CR^g_2$, $CR^g_2$C(O), CON$R^i$, N$R^i$CO, OC(O), C(O)O, C(S)O, OC(S), C(S)N$R^g$, N$R^g$C(S), $S(O)_2NR^g$, N$R^g$S(O)$_2$N=N, N$R^g$N$R^g$, N$R^g$C$R^g_2$, N$R^g$C$R^g_2$, $CR^g_2$O, OC$R^g_2$, C$R^g$=C$R^g$, C≡C, Ar or Het; a is 0, 1, 2 or 3; b is 0, 1 or 2; c is 0, 1 or 2; r is 0, 1 or 2; and u is 0 or 1; or pharmaceutically acceptable salts thereof, which are vitronectin receptor antagonists useful in the treatment of osteoporosis.




(I)

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# TITLE
Vitronectin Receptor Antagonists

## FIELD OF THE INVENTION

This invention relates to pharmaceutically active compounds which inhibit the vitronectin receptor and are useful for the treatment of diseases wherein ihibition of the vitronectin receptor is indicated, such as inflammation, cancer, angiogenesis, atherosclerosis, restenosis, and diseases wherein bone resorption is a factor.

## BACKGROUND OF THE INVENTION

Integrins are a superfamily of cell adhesion receptors, which are transmembrane glycoproteins expressed on a variety of cells. These cell surface adhesion receptors include gpIIb /IIIa, the fibrinogen receptor, and $\alpha_v\beta_3$, the vitronectin receptor. The fibrinogen receptor gpIIb /IIIa is expressed on the platelet surface and it mediates platelet aggregation and the formation of a hemostatic clot at the site of a bleeding wound. Philips, *et al., Blood.*, **1988**, *71*, 831.

The vitronectin receptor $\alpha_v\beta_3$ is expressed on a number of cells, including endothelial, smooth muscle, osteoclast, and tumor cells, and, thus, it has a variety of functions. The $\alpha_v\beta_3$ receptor expressed on the membrane of osteoclast cells is believed to play a role in the bone resportion process and contribute to the development of osteoporosis. Ross, *et al., J. Biol. Chem.*, **1987**, *262*, 7703; Fisher, *et al., Endocrinology* **1993**, *132*, 1411; Bertolini *et al., J. Bone Min. Res.*, 6, Sup. 1, S146, 252; EP 528 587 and 528 586. The $\alpha_v\beta_3$ receptor expressed on human aortic smooth muscle cells stimulates their migration into neointima, which leads to the formation of atherosclerosis and restenosis after angioplasty. Brown, *et al., Cardiovascular Res.*, **1994**, *28*, 1815. Additionally, a recent study has shown that a $\alpha_v\beta_3$ antagonist is able to promote tumor regression by inducing apoptosis of angiogenic blood vessels. Brooks, *et al., Cell*, **1994**, *79*, 1157. Thus, agents that would block the vitronectin receptor would be useful in treating diseases mediated by this receptor, such as osteoporosis, atherosclerosis, restenosis and cancer.

Alig et al., EP 0 381 033, Hartman, et al., EP 0 540,334, Blackburn, et al., WO 93/08174, Bondinell, et al., WO 95/18619, Bondinell, et al., WO 94/14776, Blackburn, et al. WO 95/04057, Egbertson, et al, EP 0 478 328, Sugihara, et al. EP 529,858, Porter, et al., EP 0 542 363, and Fisher, et al., EP 0 635 492, and many others disclose certain compounds that are useful for selectively inhibiting the fibrinogen receptor. PCT/US95/08306, filed June 29, 1995 (SmithKline Beecham Corp.) and PCT/US95/08146 filed June 29, 19951995 (SmithKline Beecham Corp.) disclose vitronectin receptor selective antagonists. However, there are few reports of compounds which are potent vitronectin receptor antagonists. It has now been discovered that certain appropriately substituted amino pyridine compounds are potent inhibitors of the vitronectin receptor. In particular, it has been discovered that the amino pyridine moiety may be combined with a fibrinogen atagonist template to prepare compounds which are more potent inhibitors of the vitronectin receptor than the fibrinogen receptor.

## SUMMARY OF THE INVENTION

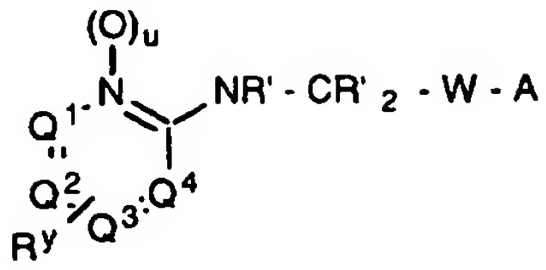
This invention comprises compounds of the formula (I) as described hereinafter, which have pharmacological activity for the inhibition of the vitronection receptor and are useful in the treatment of inflammation, cancer, cardiovascular disorders, such as atherosclerosis and restenosis, and diseases wherein bone resorption is a factor, such as osteoporosis.

This invention is also a pharmaceutical composition comprising a compound according to formula (I) and a pharmaceutically acceptable carrier.

This invention is also a method of treating diseases which are mediated by the vitronectin receptor. In a particular aspect, the compounds of this invention are useful for treating atherosclerosis, restenosis, inflammation, cancer and osteoporosis.

## DETAILED DESCRIPTION

This invention comprises novel compounds which are more potent inhibitors of the vitronectin receptor than the fibrinogen receptor. The compounds of the instant invention comprise a fibrinogen receptor antagonist template that is linked to an optionally substituted 2-pyridyl-amine moiety according to formula (I):



(I)

wherein

A is a fibrinogen antagonist template;

W is a linking moiety of the form $-(CHR^g)_a-U-(CHR^g)_b-V-$;

$Q^1$, $Q^2$ and $Q^3$ are independently N or C-$R^y$, provided that no more than one of $Q^1$, $Q^2$, $Q^3$ and $Q^4$ is N;

R' is is H or $C_{1-6}$alkyl, $C_{3-7}$cycloalkyl-$C_{0-6}$alkyl or Ar-$C_{0-6}$alkyl

$R^g$ is H or $C_{1-6}$alkyl, Het-$C_{0-6}$alkyl, $C_{3-7}$cycloalkyl-$C_{0-6}$alkyl or Ar-$C_{0-6}$alkyl;

$R^k$ is $R^g$, $-C(O)R^g$ or $-C(O)OR^g$

$R^i$ is H, $C_{1-6}$alkyl, Het-$C_{0-6}$alkyl, $C_{3-7}$cycloalkyl-$C_{0-6}$alkyl, Ar-$C_{0-6}$alkyl, Het-$C_{0-6}$alkyl-U'-$C_{1-6}$alkyl, $C_{3-7}$cycloalkyl-$C_{0-6}$alkyl-U'-$C_{1-6}$alkyl or Ar-$C_{0-6}$alkyl-U'-$C_{1-6}$alkyl;

$R^y$ is H, halo, $-OR^g$, $-SR^g$, -CN, $-NR^gR^k$, $-NO_2$, $-CF_3$, $CF_3S(O)_r-$, $-CO_2R^g$, $-COR^g$ or

$-CONR^g{}_2$, or $C_{1-6}$alkyl optionally substituted by halo, $-OR^g$, $-SR^g$, -CN, $-NR^gR''$, $-NO_2$, $-CF_3$, R'S(O)$_3$-, $-CO_2R^g$, $-COR^g$ or $-CONR^g{}_2$;

U and V are absent or CO, $CR^g{}_2$, $C(=CR^g{}_2)$, $S(O)_c$, O, $NR^g$, $CR^gOR^g$, $CR^g(OR^k)CR^g{}_2$, $CR^g{}_2CR^g(OR^k)$, $C(O)CR^g{}_2$, $CR^g{}_2C(O)$, $CONR^i$, $NR^iCO$, OC(O), C(O)O, C(S)O, OC(S), C(S)$NR^g$, $NR^gC(S)$, $S(O)_2NR^g$, $NR^gS(O)_2$ N=N, $NR^gNR^g$, $NR^gCR^g{}_2$, $NR^gCR^g{}_2$, $CR^g{}_2O$, $OCR^g{}_2$, $CR^g$=$CR^g$, C≡C , Ar or Het;

a is 0, 1, 2 or 3;

b is 0, 1 or 2;

c is 0, 1 or 2;

u is 0 or 1;

and pharmaceutically acceptable salts thereof.

Preferably, $Q^1$, $Q^2$, $Q^3$ and $Q^4$ are all CH, and u is 0.

Suitably, R' is H and R" is H or $C_{1-4}$alkyl.

Suitably, W is $-(CHR^g)_a-CONR^i-$ or $-(CHR^g)_a-NR^iCO-$

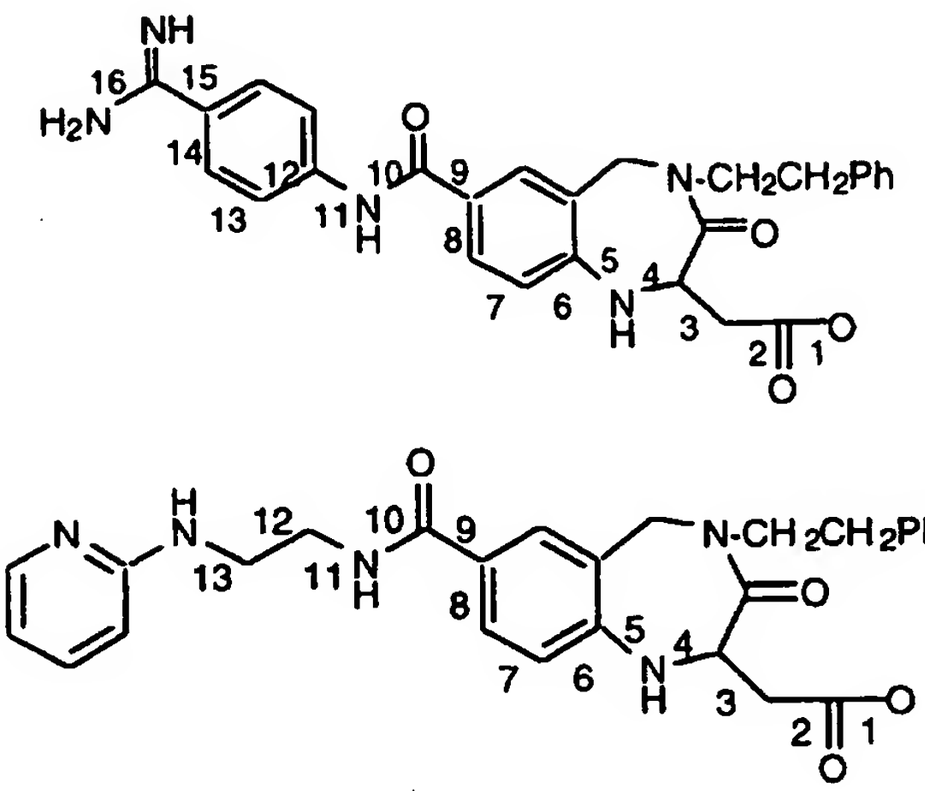
A fibrinogen receptor antagonist is an agent that inhibits the binding of fibrinogen to the platelet-bound fibrinogen receptor GPIIb-IIIa. Many fibrinogen antagonists are known to the art. As used herein, the term "fibrinogen receptor antagonist template"

means the core structure of a fibrinogen receptor antagonist, said core containing an acidic group and being linked to an organic group substituted with a basic nitrogen moiety. Typically, the core structure adds some form of rigid spacing between the acidic moiety and the basic nitrogen moiety, and contains one or more ring structures or amide bonds to effect this. It is preferred that about twelve to fifteen, more preferably thirteen or fourteen, intervening covalent bonds via the shortest intramolecular path will exist between the acidic group of the fibrinogen receptor antagonist template and nitrogen of the *o*-amino substituent on the pyridine moiety in formula (I). It is an object of this invention that a fibrinogen receptor antagonist is converted to a vitronectin receptor antagonist by replacing the basic nitrogen group in a fibrinogen receptor antagonist with an optionally substituted pyrid-2-yl-amino group. In addition, the number of intervening covalent bonds between the acidic moiety and the nitrogen of the *o*-amino substituent on the pyridine ring will be about two to five, preferably three or four, covalent bonds shorter than the number of intervening covalent bonds between the acidic moiety and the basic nitrogen group of the fibrinogen antagonist. The identity of the linking moiety W may be chosen to obtain the proper spacing between the acidic moiety of the fibrinogen antagonist template and the nitrogen atom of the pyridine. Generally, a fibrinogen antagonist will have an intramolecular distance of about 16 angstroms between the acidic moiety (e.g., the atom which gives up the proton or accepts the electron pair) and the basic moiety (e.g., which accepts a proton or donates and electron pair), while the vitronectin antagonist will have about 14 angstroms between the respective acidic and basic centers.

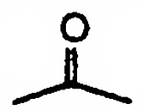
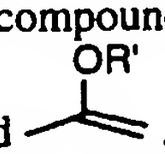
For purposes of illustration, using the 7-2,3,4,5-tetrahydro-3-oxo-4-methyl-benzodiazepine fibrinogen antagonist template disclosed in WO 93/08174 as a suitable fibrinogen antagonist template, the compound (R,S)-7-[[[4-(aminoiminomethyl)phenyl] amino]carbonyl]-4-(2-phenylethyl)-1,3,4,5-tetrahydro-3-oxo-2H-1,4-benzodiazepine-2-acetic acid, which is potent and selective fibrinogen antagonist, is converted to a potent and selective vitronectin receptor antagonist by replacing the 4-(aminoiminomethyl)phenyl moiety with the (pyrid-2-yl)ethyl moiety. As illustrated below in Figure 1, in the former case, there are sixteen intervening covalent bonds between the acidic moiety and the basic moiety; in the fibrinogent antagonist whereas, in

the latter case there are 13 intervening covalent bonds in the vitronectin antagonist of this invention.

Figure 1




In fact the 4-(aminoiminomethyl)phenyl moiety is a common substituent on fibrinogen antagonist templates known to the art, and simple replacement of this moiety with an optionally substituted (pyrid-2-yl)aminoethyl moiety may serve as guide to converting compounds having known fibrinogen antagonist templates into vitronectin receptor antagonists.

Also included in this invention are pharmaceutically acceptable addition salts, complexes or prodrugs of the compounds of this invention. Prodrugs are considered to be any covalently bonded carriers which release the active parent drug according to formula (I) *in vivo*. In cases wherein the compounds of this invention may have one or more chiral centers, unless specified, this invention includes each unique nonracemic compound which may be synthesized and resolved by conventional techniques. In cases in which compounds have unsaturated carbon-carbon double bonds, both the cis (Z) and trans (E) isomers are within the scope of this invention. In cases wherein compounds may exist in tautomeric forms, such as keto-enol tautomers, such as  and  , and each tautomeric form is contemplated as being included within this invention whether existing in equilibrium or locked in one form by appropriate substitution with R'.



The compounds of formula (I) inhibit the binding of vitronectin and other RGD-containing peptides to the vitronectin ($\alpha_v\beta_3$) receptor. Inhibition of the vitronectin

receptor on osteoclasts inhibits osteoclastic bone resorption and is useful in the treatment of diseases wherein bone resorption is associated with pathology, such as osteoporosis. Additionally, since the compounds of the instant invention inhibit vitronectin receptors on a number of different types of cells, said compounds would be useful in the treatment of inflammation and cardiovascular diseases, such as atherosclerosis and restenosis, and would be useful as anti-metastatic and antitumor agents.

Table I, below, describes certain fibrinogen receptor antagonists, whose core structures are useful in carrying out the instant invention. Reference should be made to the patent applications and other publications for their full disclosures, including the methods of preparing said templates and specific compounds embodying said templates. The entire disclosure of the noted patent applications and other publications is incorporated herein by reference as though fully set forth. The list following is not intended to limit the scope of the present invention, but only to illustrate certain known templates.

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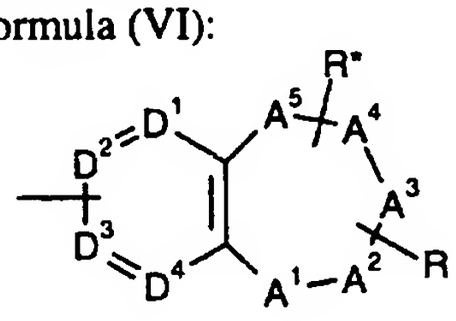
In one particular embodiment, the fibrinogen receptor antagonist template A is the fused 6/7 ring bicyclic ring defined in Bondinell, et al., WO 93/00095, published January 7, 1993, as defined by sub-formula (VI):



(II)

wherein

$A^1$ to $A^5$ form an accessible substituted seven-membered ring, which may be saturated or unsaturated, optionally containing up to two heteroatoms chosen from the group of O, S and N wherein S and N may be optionally oxidized;

$D^1$ to $D^4$ form an accessible substituted six membered ring, optionally containing up to two nitrogen atoms;

R is at least one substituent chosen from the group of $R^7$, or Q-$C_{1-4}$alkyl, Q-$C_{2-4}$alkenyl, Q-$C_{2-4}$alkynyl, optionally substituted by one or more of =O, $R^{11}$ or $R^7$;

$R^*$ is H, Q-$C_{1-6}$alkyl, Q-$C_{1-6}$oxoalkyl, Q-$C_{2-6}$alkenyl, Q-$C_{3-4}$oxoalkenyl, Q-$C_{3-4}$oxoalkynyl, Q-$C_{2-4}$alkynyl, $C_{3-6}$cycloalkyl, Ar or Het, optionally substituted by one or more of $R^{11}$;

Q is H, $C_{3-6}$cycloalkyl, Het or Ar;

$R^7$ is $-COR^8$, $-COCR'_2R^9$, $-C(S)R^8$, $-S(O)_mOR'$, $-S(O)_mNR'R''$, $-PO(OR')$, $-PO(OR')_2$, $-B(OR')_2$, $-NO_2$ and Tet;

$R^8$ is $-OR'$, $-NR'R''$, $-NR'SO_2R'$, $-NR'OR'$, $-OCR'_2C(O)OR'$, $-OCR'_2OC(O)-R'$, $-OCR'_2C(O)NR'_2$, $CF_3$ or $AA^1$;

$R^9$ is $-OR'$, $-CN$, $-S(O)_rR'$, $S(O)_mNR'_2$, $-C(O)R'$ $C(O)NR'_2$ or $-CO_2R'$;

$R^{11}$ is H, halo, $-OR^{12}$, $-CN$, $-NR'R^{12}$, $-NO_2$, $-CF_3$, $CF_3S(O)_r$, $-CO_2R'$, $-CONR'_2$, Q-$C_{0-6}$alkyl-, Q-$C_{1-6}$oxoalkyl-, Q-$C_{2-6}$alkenyl-, Q-$C_{2-6}$alkynyl-, Q-$C_{0-6}$alkyloxy-, Q-$C_{0-6}$alkylamino- or Q-$C_{0-6}$alkyl-$S(O)_r$-;

$R^{12}$ is R', $-C(O)R'$, $-C(O)NR'_2$, $-C(O)OR^{15}$, $-S(O)_mR'$ or $S(O)_mNR'_2$;

$R^{13}$ is R', $-CF_3$, $-SR'$, or $-OR'$;

$R^{14}$ is R', C(O)R', CN, $NO_2$, $SO_2R'$ or $C(O)OR^{15}$;

$R^{15}$ is H, $C_{1-6}$alkyl or Ar-$C_{0-4}$alkyl;

R' is H, $C_{1-6}$alkyl, $C_{3-7}$cycloalkyl-$C_{0-4}$alkyl or Ar-$C_{0-4}$alkyl;

R" is R', $-C(O)R'$ or $-C(O)OR^{15}$;

R"' is R" or AA2;

AA1 is an amino acid attached through its amino group and having its carboxyl group optionally protected, and AA2 is an amino acid attached through its carboxyl group, and having its amino group optionally protected;

m is 1 or 2;

n is 0 to 3;

p is 0 or 1; and

t is 0 to 2; or

pharmaceutically acceptable salts thereof.

With reference to formula (II), suitably,

$A^1$ is $CR^1R^{1'}$, $CR^1$, $NR^1$, N, O or $S(O)_x$;

$A^2$ is $CR^2R^{2'}$, $CR^2$, $NR^2$;

$A^3$ is $CR^3R^{3'}$, $CR^3$, $NR^3$, N, O or $S(O)_x$;

$A^4$ is $CR^4R^{4'}$, $CR^4$, $NR^4$, or N;

$A^5$ is $CR^5R^{5'}$, $CR^5$, $NR^5$, N, O or $S(O)_x$;

$D^1$-$D^4$ are $CR^{11}$, $CR^6$ or N;

$R^1$ and $R^{1'}$ are $R^*$ or R, or together are =O;

$R^2$ and $R^{2'}$ are $R^*$, R or =O;

$R^3$ and $R^{3'}$ are $R^*$, R or =O;

$R^4$ and $R^{4'}$ are $R^*$, R or =O;

$R^5$ and $R^{5'}$ are $R^*$, R or =O; and

x is 0 to 2.

More suitably, $A^1$ is $CR^1R^{1'}$, $CR^1$, $NR^1$, N, O or S; $A^2$ is $CR^2R^{2'}$, $NR^2$ or $CR^2$; $A^3$ is $CR^3R^{3'}$; $A^4$ is $CR^4R^{4'}$, $CR^4$, $NR^4$, or N; $A^5$ is $CR^5R^{5'}$, $CR^5$, $NR^5$, N, O; $D^1$ - $D^4$ are CH; $R^2$ or $R^4$ are R; $R^3$,$R^{3'}$ and $R^5$,$R^{5'}$ are =O or $R^*$,H.

Preferably, $A^1$ is $CHR^1$, $CR^1$, $NR''$, N or S; $A^2$ is $CR^2$ or $CR^2R^{2'}$; $A^3$ is $CR^3R^{3'}$; $A^4$ is $CR^4R^{4'}$ or $NR^4$; $A^5$ is $CR^5R^{5'}$, and $D^1$ - $D^4$ are CH.

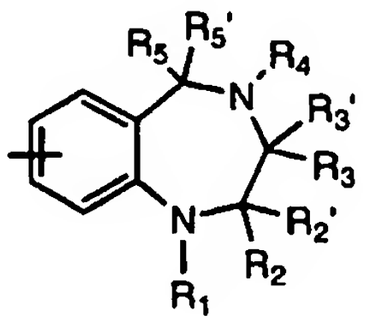
In one embodiment, $A^1$ is $CR^1$, $A^2$ is $CR^2$, $A^3$ is C=O, $A^4$ is $NR^4$ and $A^5$ are $CHR^5$.

In another embodiment, $A^1$ is $NR^1$, $A^2$ is $CHCR^2$, $A^3$ is $CR^3R^{3'}$, $A^4$ is $NR^4$, and $A^5$ are C=O.

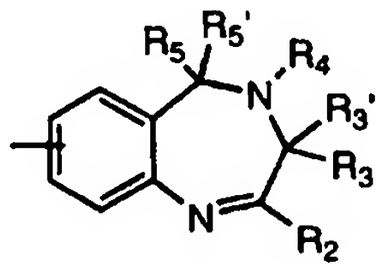
In yet another embodiment, $A^1$ and $A^4$ are C=O, $A^2$ is $NR^2$, $A^3$ is $CHR^{3'}$ and $A^5$ is $NR^5$.

In a preferred embodiment, $A^1$ is $NR^1$, $A^2$ is $CHR^2$, $A^3$ is C=O, $A^4$ is $NR'$ and $A^5$ is $CHR^5$.

Representative sub-formulas of (II) are given by each of formulas (IIa)-(IIi) below:



(IIa)



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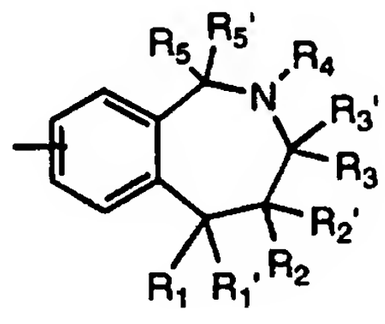
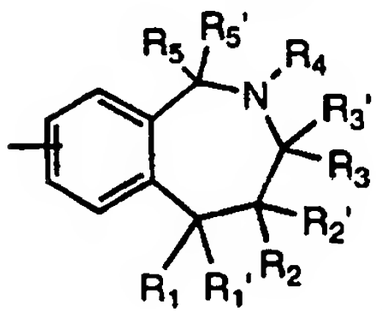
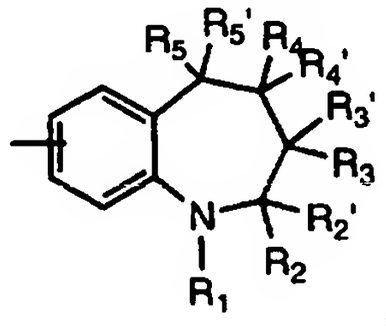


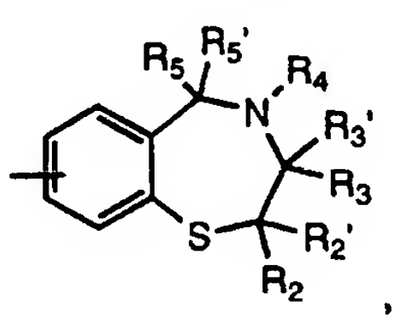
(IIc)



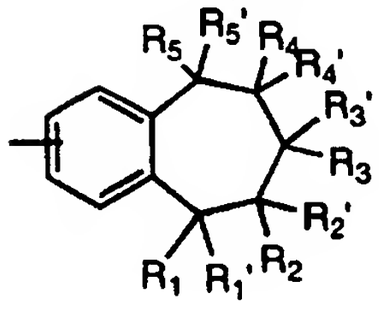
(IId)



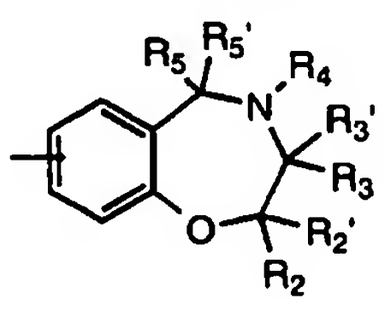
(IIe)



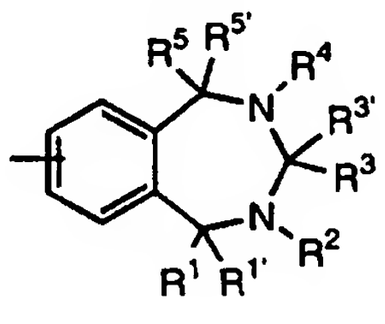
(IIf)



(IIg)

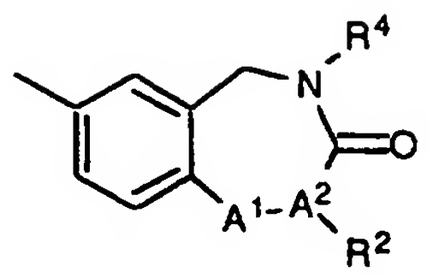


(IIh)



(IIi)

A preferred template is given by formula (III):



(III)

wherein

$A^1$-$A^2$ is $NR^1$-CH, $NC(O)R^3$-CH, N=C, $CR^1$=C, $CHR^1$-CH, O-CH or S-CH;

$R^1$ is H, $C_{1-6}$ alkyl or benzyl;

$R^2$ is $(CH_2)_qCO_2H$;

$R^4$ is H, $C_{1-6}$alkyl, Ar-$C_{0-6}$alkyl, Het-$C_{0-6}$alkyl, or $C_{3-6}$cycloalkyl-$C_{0-6}$alkyl; and

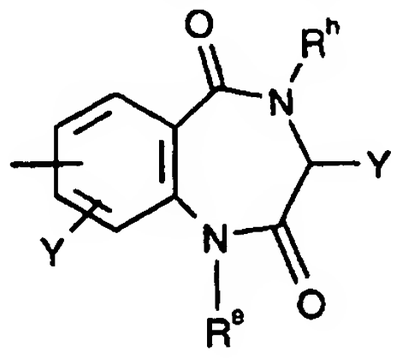
q is 1, 2 or 3.

Preferably $A^1$-$A^2$ is NH-CH and $R^2$ is $CH_2CO_2H$. Suitably, $R^3$ is methyl and W (as defined in formula (I)) is $CH_2NR'CO$. Suitably $R^i$ is substituted by NHR', CN, $CO_2H$, biotin, benzimidazole or optionally substituted phenyl.

Specific examples of vitronectin antagonists employing this template are:
(S)-2,3,4,5-Tetrahydro-4-methyl-3-oxo-7-[[[2-[2-(pyridinyl)amino]ethyl]amino] carbonyl]-1H-1,4-benzodiazepine-2-acetic acid;
(S)-2,3,4,5-Tetrahydro-4-methyl-3-oxo-7-[[[2-[(1-oxo-2-pyridinyl)amino]ethyl] amino]carbonyl]-1H-1,4-benzodiazepine-2-acetic acid;
(S)-2,3,4,5-Tetrahydro-3-oxo-7-[[[2-[2-(pyridinyl)amino]ethyl]amino]carbonyl]-1H-1,4-benzodiazepine-2-acetic acid;
(S)-2,3,4,5-Tetrahydro-3-oxo-7-[[2-[2-(pyridinyl)amino]ethyl]amino]carbonyl]-4-(2,2,2-trifluoroethyl)-1H-1,4-benzodiazepine-2-acetic acid;
(±)-2,3,4,5-Tetrahydro-3-oxo-4-(phenylethyl)-7-[[[2-[2-(pyridinyl)amino]ethyl]amino]carbonyl]-1H-1,4-benzodiazepine-2-acetic acid;
(S)-2,3,4,5-Tetrahydro-4-methyl-7-[[[2-[2-(6-methyl-pyridinyl)amino]ethyl]amino]carbonyl]-3-oxo-1H-1,4-benzodiazepine-2-acetic acid;
(S)-2,3,4,5-Tetrahydro-4-methyl-3-oxo-7-[[[2-[2-(pyridinyl)amino]ethyl]methylamino]carbonyl]-1H-1,4-benzodiazepine-2-acetic acid;
(±)-2,3,4,5-Tetrahydro-4-methyl-3-oxo-7-[[[2-[2-(pyrimidinyl)amino]ethyl]amino] carbonyl]-1H-1,4-benzodiazepine-2-acetic acid;
(±)-2,3,4,5-Tetrahydro-4-methyl-7-[[2-[(6-methyl-3-pyridazinyl)amino]ethyl]amino] carbonyl]-3-oxo-1H-1,4-benzodiazepine-2-acetic acid; and
(±)-2,3,4,5-Tetrahydro-4-methyl-3-oxo-7-[[2-[3-(pyridazinyl)amino]ethyl]amino] carbonyl]-1H-1,4-benzodiazepine-2-acetic acid.

A preferred compound is (S)-2,3,4,5-Tetrahydro-4-methyl-3-oxo-7-[[[2-[2-(pyridinyl)amino]ethyl]amino] carbonyl]-1H-1,4-benzodiazepine-2-acetic acid.

Another embodiment of a benzodiazepine fibrinogen receptor template A is represented by the 1,4-benzodiazepine 2,5-dione of sub-formula (IV);



(IV)

wherein:

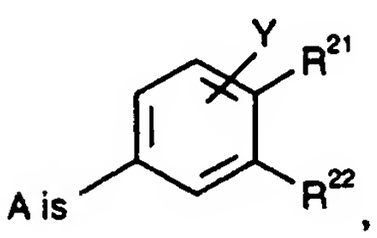
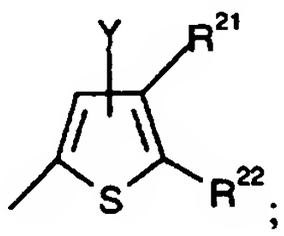
Y is H, $C_{1-4}$alkyl, $C_{1-4}$alkoxy, $C_{1-4}$alkoxycarbonyl, F, Cl, Br, I, $CF_3$, $OR^f$, $S(O)_kR^f$, $COR^f$, $NO_2$, $N(R^f)_2$, $CO(NR^f)_2$, $CH_2N(R^f)_2$, methylenedioxy, CN, $CO_2R^f$, $OC(O)R^f$, or $NHC(O)R^f$; and

$R^h$ is $(CH_2)_qCO_2R^f$.

Suitably $R^h$ is $CH_2CH_2CO_2H$.

Entries (V)-(XV) in Table II summarize other illustrative fibrinogen receptor templates that are included within the scope of the present invention:

Table II

| | |
|---|---|
| (V) | A is  or  |

wherein:

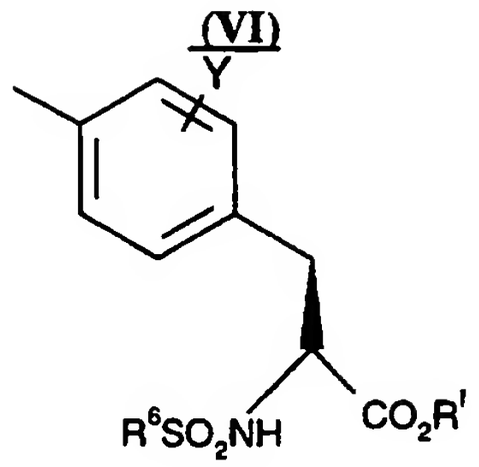
$R^{21}$ and $R^{22}$ independently are H or -Z-$CO_2R^f$or Z-$CON(R^f)_2$ with the proviso that one of $R^{21}$ or $R^{22}$ is -Z-$CO_2R^f$ or Z-$CON(R^f)_2$;

Z is -$CH_2$-, -$O(CH_2)_q$-, -$NR^f(CH_2)_q$-, -$S(CH_2)_q$, -$CH_2CH_2$-, -$CH(CH_3)CH_2$-, -$(CH_2)_3$-, -CH=CH-, -$C(CH_3)$=CH-, $CH_2$-CH=CH- or CH=$CHCH_2$; and

Y is H, $C_{1-4}$alkyl, $C_{1-4}$alkoxy, $C_{1-4}$alkoxycarbonyl, F, Cl, Br, I, $CF_3$, $OR^f$, $S(O)_kR^f$, $COR^f$, $NO_2$, $N(R^f)_2$, $CO(NR^f)_2$, $CH_2N(R^f)_2$, methylenedioxy or Z-$COR^f$,

disclosed in Alig, et al., EP 0 381 033, published August 8, 1990.

(VI)



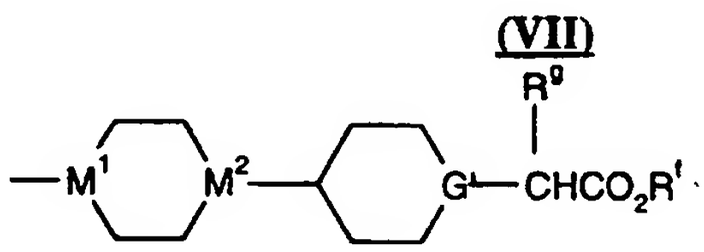
wherein:

$R^6$ is aryl, $C_{1-10}$alkyl, $C_{3-6}$cycloalkyl, $C_{4-10}$aralkyl, $C_{1-10}$alkoxyalkyl, $C_{1-10}$alkaryl, $C_{1-10}$alkylthioalkyl, $C_{1-10}$alkoxythioalkyl, $C_{1-10}$alkylamino, $C_{4-10}$aralkylamino, $C_{1-10}$alkanoylamino, $C_{4-10}$aralkanoylamino, $C_{1-10}$alkanoyl, $C_{4-10}$aralkanoyl, or $C_{1-10}$carboxyalkyl; and

Y is H, $C_{1-4}$alkyl, $C_{1-4}$alkoxy, $C_{1-4}$alkoxycarbonyl, F, Cl, Br, I, $CF_3$, $OR^f$, $S(O)_kR^f$, $COR^f$, $NO_2$, $N(R^f)_2$, $CO(NR^f)_2$, $CH_2N(R^f)_2$, methylenedioxy, CN, $CO_2R^f$, $OC(O)R^f$, or $NHC(O)R^f$,

disclosed in Egbertson, et al., EP 0 478 328, published April 1, 1992.

(VII)



wherein:

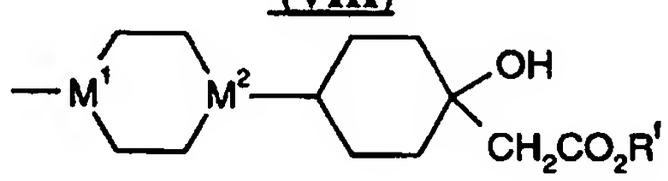
$M^1$ is CH or N;

$M^2$ is CH or N, with the proviso that when $M^1$ is CH, $M^2$ is N; and

G' is N or $N^{\oplus}R''$,

disclosed in Eldred, et al., EP 0542 363, published May 19, 1993.

(VIII)



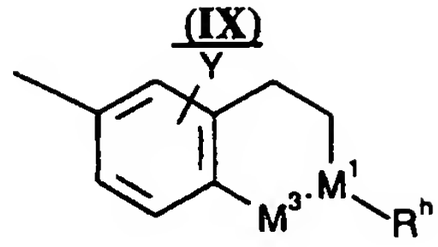
wherein:

$M^1$ is CH or N; and

$M^2$ is CH or N, with the proviso that when $M^1$ is CH, $M^2$ is N,

disclosed in Porter, et al., EP 0 537 980, published April 21, 1993.

(IX)



wherein:

$M^1$ is CH or N;

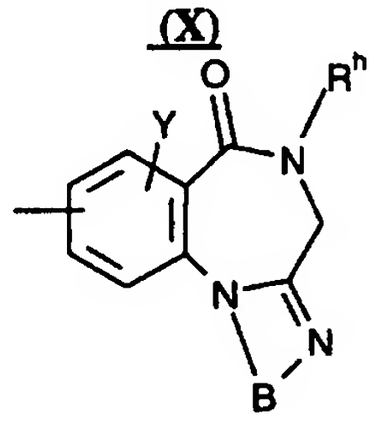
Y is H, $C_{1-4}$alkyl, $C_{1-4}$alkoxy, $C_{1-4}$alkoxycarbonyl, F, Cl, Br, I, $CF_3$, $OR^f$, $S(O)_kR^f$, $COR^f$, $NO_2$, $N(R^f)_2$, $CO(NR^f)_2$, $CH_2N(R^f)_2$, methylenedioxy, CN, $CO_2R^f$, $OC(O)R^f$, or $NHC(O)R^f$;

$D^3$ is $CH_2$ or C=O; and

$R^h$ is $(CH_2)_qCO_2R^f$,

disclosed in Klinnick, et al., EP 0 635,492, published January 25, 1995.

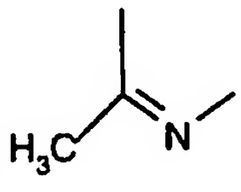
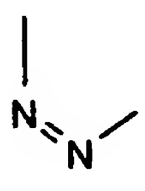
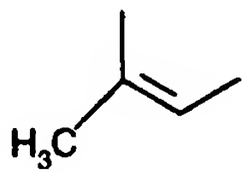
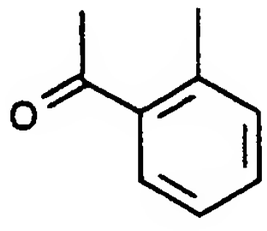
(X)



wherein:

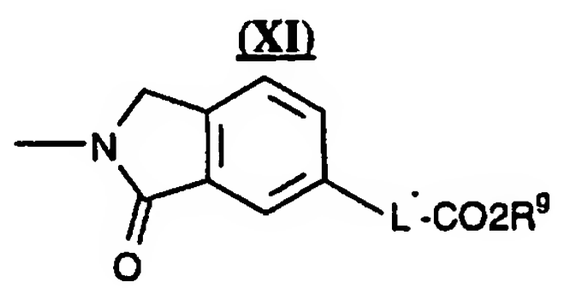
Y is H, $C_{1-4}$alkyl, $C_{1-4}$alkoxy, $C_{1-4}$alkoxycarbonyl, F, Cl, Br, I, $CF_3$, $OR^f$, $S(O)_kR^f$, $COR^f$, $NO_2$, $N(R^f)_2$, $CO(NR^f)_2$, $CH_2N(R^f)_2$, methylenedioxy, CN, $CO_2R^f$, $OC(O)R^f$, or $NHC(O)R^f$;

$R^h$ is $(CH_2)_nCO_2R^f$; and

B is  ,  ,  , or 

disclosed in Blackburn, et al., WO 95/04057, published February 9, 1995.

(XI)

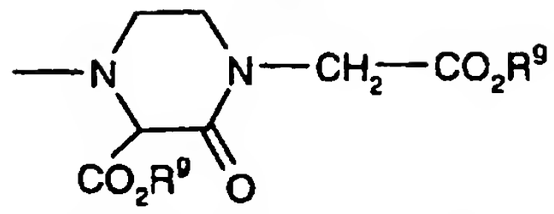


wherein:

L* is $-C(O)NR^g-(CH_2)-$, $-C(O)-(CH_2)_q-$, $NR^g-(CH_2)_q-$, $-O-(CH_2)_q-$, or $S(O)_k-(CH_2)_q-$,

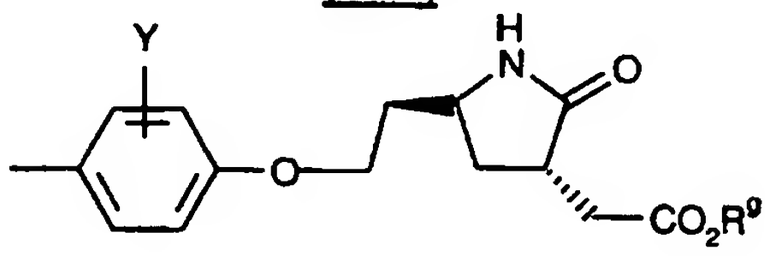
disclosed in Hartman, et al., EP 0 540 331, published May 5, 1993.

(XII)



disclosed in Sugihara, et al., EP 0 529,858, published March 3, 1993.

(XIII)

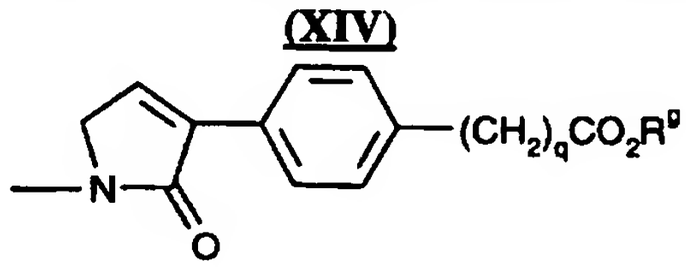


wherein:

Y is H, $C_{1-4}$alkyl, $C_{1-4}$alkoxy, $C_{1-4}$alkoxycarbonyl, F, Cl, Br, I, $CF_3$, $OR^f$, $S(O)_kR^f$, $COR^f$, $NO_2$, $N(R^f)_2$, $CO(NR^f)_2$, $CH_2N(R^f)_2$, methylenedioxy, CN, $CO_2R^f$, $OC(O)R^f$, or $NHC(O)R^f$,

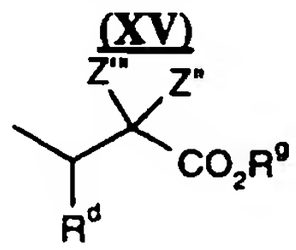
disclosed in Himmeisbach, et al., EP 0 483 667, published May 6, 1992.

(XIV)



disclosed in Linz, et al., EP 0 567 968, published November 3, 1993.

(XV)



wherein:

$R^d$ is Het-$C_{0-6}$alkyl; and

Z", Z'" independently are hydrogen, $C_{1-4}$alkyl, halo, $OR^f$, CN, $S(O)_kR^f$, $CO_2R^f$, or OH,

disclosed in Bovy, et al., EP 0 539 343, published April 28, 1993.

The above descriptions of fibrinogen receptor templates for use in the present invention were taken from pending published patent applications. Reference should be made to such patent applications for their full disclosures, including the variations possible for such templates and methods of preparing said templates, the entire disclosure of such patent applications being incorporated herein by reference.

In cases wherein the compounds of this invention may have one or more chiral centers, unless specified, this invention includes each unique nonracemic compound which may be synthesized and resolved by conventional techniques. In cases in which compounds have unsaturated carbon-carbon double bonds, both the cis (Z) and trans (E)

isomers are within the scope of this invention. The meaning of any substituent at any one occurrence is independent of its meaning, or any other substituent's meaning, at any other occurrence.

Abbreviations and symbols commonly used in the peptide and chemical arts are used herein to describe the compounds of this invention. In general, the amino acid abbreviations follow the IUPAC-IUB Joint Commission on Biochemical Nomenclature as described in *Eur. J. Biochem.*, 158, 9 (1984).

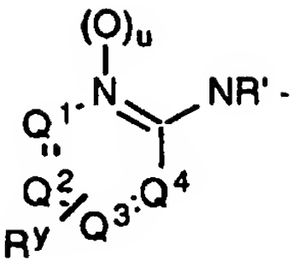
$C_{1-4}$alkyl as applied herein means an optionally substituted alkyl group of 1 to 4 carbon atoms, and includes methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl and t-butyl. $C_{1-6}$alkyl additionally includes pentyl, n-pentyl, isopentyl, neopentyl and hexyl and the simple aliphatic isomers thereof. $C_{0-4}$alkyl and $C_{0-6}$alkyl additionally indicates that no alkyl group need be present (*e.g.*, that a covalent bond is present).

Any $C_{1-4}$alkyl or $C_{1-6}$ alkyl, $C_{2-6}$ alkenyl, $C_{2-6}$ alkynyl or $C_{1-6}$ oxoalkyl may be optionally substituted with the group $R^x$, which may be on any carbon atom that results in a stable structure and is available by conventional synthetic techniques. Suitable groups for $R^x$ are $C_{1-4}$alkyl, OR', SR', $C_{1-4}$alkyl, $C_{1-4}$alkylsulfonyl, $C_{1-4}$alkylsulfoxyl, -CN, $N(R')_2$, $CH_2N(R')_2$, $-NO_2$, $-CF_3$, $-CO_2$ R', $-CON(R')_2$, -CO R', -N R'C(O) R', OH, F, Cl, Br, I, $N_3$ or $CF_3S(O)_r$-,wherein r is 0 to 2 and R' is as defined with respect to formula (II).

Ar, or aryl, as applied herein, means phenyl or naphthyl, or phenyl or naphthyl substituted by one to three substituents, such as those defined above for alkyl, especially $C_{1-4}$alkyl, $C_{1-4}$alkoxy, $C_{1-4}$alkthio, $CO_2H$, $N_3$, trifluoroalkyl, OH, F, Cl, Br or I.

Het, or heterocycle, indicates an optionally substituted five or six membered monocyclic ring, or a nine or ten-membered bicyclic ring containing one to three heteroatoms chosen from the group of nitrogen, oxygen and sulfur, which are stable and available by conventional chemical synthesis. Illustrative heterocycles are benzofuryl, benzimidazole, benzopyran, benzothiophene, biotin, furan, imidazole, indoline, morpholine, piperidine, piperazine, pyrrole, pyrrolidine, tetrahydropyridine, pyridine, thiazole, thiophene, quinoline, isoquinoline, and tetra- and perhydro- quinoline and isoquinoline. Any accessible combination of up to three substituents on the Het ring, such as those defined above for alkyl that are available by chemical synthesis and are stable are within the scope of this invention.

$C_{3-7}$cycloalkyl refers to an optionally substituted carbocyclic system of three to seven carbon atoms, which may contain up to two unsaturated carbon-carbon bonds. Typical of $C_{3-7}$cycloalkyl are cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl and cycloheptyl. Any combination of up to three substituents, such as those defined above for alkyl, on the cycloalkyl ring that is available by conventional chemical synthesis and is stable, is within the scope of this invention.

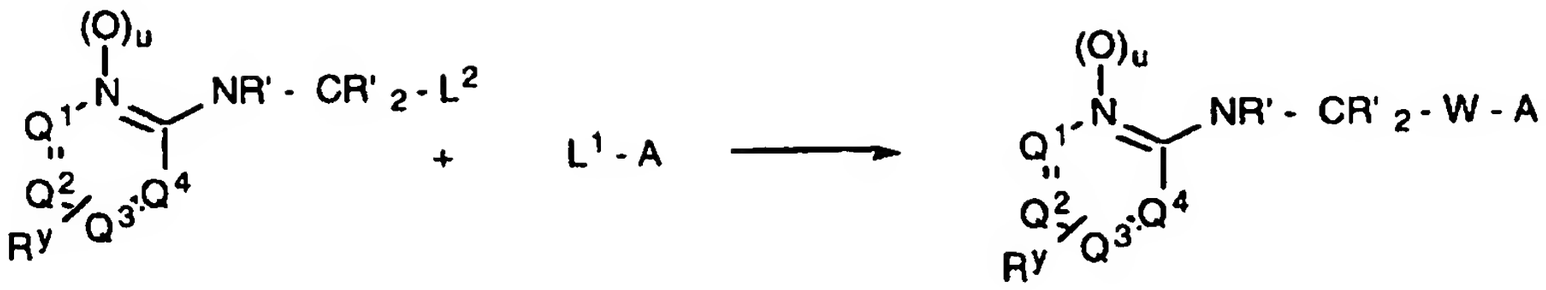


The ring represented by is a six-membered ring containing at least one nitrogen which is substituted in the 2 position with a nitrogen atom. The ring may optionally have an additional nitrogen atom in the ring, and hence may be a pyrazine, pyridazine or a pyrimidine. The substituent $R^y$ may be in any position on $Q^1$ - $Q^4$ which results in a stable structure. It will be apparent that when the value of u is 1 the compound described will be an N-oxide; whereas, when the value of u is 0 there is no oxygen substituent on the nitrogen. A pyridine ring is preferred.

Certain radical groups are abbreviated herein. t-Bu refers to the tertiary butyl radical, Boc refers to the t-butyloxycarbonyl radical, Fmoc refers to the fluorenylmethoxycarbonyl radical, Ph refers to the phenyl radical, Cbz refers to the benzyloxycarbonyl radical, BrZ refers to the o-bromobenzyloxycarbonyl radical, ClZ refers to the o-chlorobenzyloxycarbonyl radical, Bzl refers to the benzyl radical, 4-MBzl refers to the 4-methyl benzyl radical, Me refers to methyl, Et refers to ethyl, Ac refers to acetyl, Alk refers to $C_{1-4}$alkyl, Nph refers to 1- or 2-naphthyl and cHex refers to cyclohexyl. Tet refers to 5-tetrazolyl.

Certain reagents are abbreviated herein. DCC refers to dicyclohexylcarbodiimide, DMAP refers to dimethylaminopyridine, DIEA refers to diisopropylethyl amine, EDC refers to 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide, hydrochloride. HOBt refers to 1-hydroxybenzotriazole, THF refers to tetrahydrofuran, DIEA refers to diisopropylethylamine, DME refers to dimethoxyethane, DMF refers to dimethylformamide, NBS refers to N-bromosuccinimide, Pd/C refers to a palladium on carbon catalyst, PPA refers to 1-propanephosphonic acid cyclic anhydride, DPPA refers to diphenylphosphoryl azide, BOP refers to benzotriazol-1-yloxy-tris(dimethyl-amino)phosphonium hexafluorophosphate, HF refers to hydrofluoric acid, TEA refers to triethylamine, TFA refers to trifluoroacetic acid, PCC refers to pyridinium chlorochromate.

Compounds of the formula (I) are generally prepared by reacting a compound of formula (XVI) with a compound of formula (XVII), wherein $L^1$ and $L^2$ are groups which may react to form a covalent bond in the moiety W, by methods generally known in the art.



(XVI) (XVII) (I)

Typical methods include coupling to form amide bonds, nucleophilic displacement reactions and palladium catalyzed couplings.

For instance, when W contains an ether or amine linkage, the bond may be formed by a displacement reaction, and one of $L^1$ and $L^2$ will contain an amino or hydroxy group and the other will contain a displaceable group, such as a chloro, bromo or iodo group. When W contains an amide bond, typically one of $L^1$ and $L^2$ will contain an amino group, and the other will contain a carboxylic acid group. In another approach, $L^1$ may be an aryl or heteroaryl bromide, iodide or trifluoromethylsulfonyloxy derivative and $L^2$ may contain an amino group and the amide linkage may be formed by palladium-catalyzed aminocarbonylation with carbon monoxide in a suitable solvent such as dimethylformamide or toluene.

It will be apparent that the precise identity of $L^1$ and $L^2$ will be dependent upon the site of the linkage being formed. General methods for preparing the linkage -$(CHR")_r$-U-$(CHR")_s$-V- are described, for example, in EP-A 0 372 486 and EP-A 0 381 033 and EP-A 0 478 363, which are incorporated herein by reference.

For instance, if V is CONH, $L^1$ may be $-NH_2$, $L^2$ may be OH (as in an acid) or Cl (as in an acid chloride). For instance, (pyrid-2-yl) aminomethyl$(CH_2)_a$-COCl may be reacted with a suitable amine. When $L^2$ is OH, a coupling agent is used.

Similarly, if V is NHCO, $L^1$ may be $-CO_2H$ or CO-Cl, $L^2$ may be $-NH_2$. For instance, (pyrid-2-yl)aminomethyl$(CH_2)_a$-NHR' may be reacted with a suitable carboxyolic acid.

Where V is $NHSO_2$, $L^1$ may be $SO_2Cl$, $L^2$ may be $-NH_2$ as above. Where V is $SO_2NH$, $L^1$ may be $-NH_2$ and $L^2$ may be $SO_2Cl$. Methods to prepare such sulfonyl chlorides are disclosed, for instance, in *J. Org. Chem.*, 23, 1257 (1958).

If V is CH=CH, $L^1$ may be -CHO, $L^2$ may be CH=P-$Ph_3$. Alternately, $L^1$ may be CH=P-$Ph_3$ and $L^2$ may be CHO. For instance, (pyrid-2-yl)aminomethyl $(CH_2)_a$-CHO may be reacted with a suitable phosphorane.

Where V is $CH_2CH_2$ may be obtained by reduction of a suitably protected compound wherein V is CH=CH.

Where V is $CH_2O$, $CH_2N$ or C≡C, $L^1$ may be -OH, -NH or -C≡CH,respectively; $L^2$ may be -Br or -I. Similarly where U or V is $OCH_2$, NR'$CH_2$ or C≡C, $L^1$ may be -$CH_2$Br and $L^2$ may be -OH, -NH or -C≡CH, respectively. For example, (pyrid-2-yl)aminomethyl$(CH_2)_a$-Br may be reacted with an appropriate amine. alkoxide or acetylene. Alternately, when U or V is C≡C, $L^1$ may be Br, I or $CF_3SO_3$, $L^2$ may be C≡CH and the coupling may be catalyzed by palladium and a base.

Compounds wherein V is $CHOHCH_2$ may be prepared from a suitably protected compound where V is CH=CH by the procedure disclosed in *J. Org. Chem.*, 54, 1354 (1989).

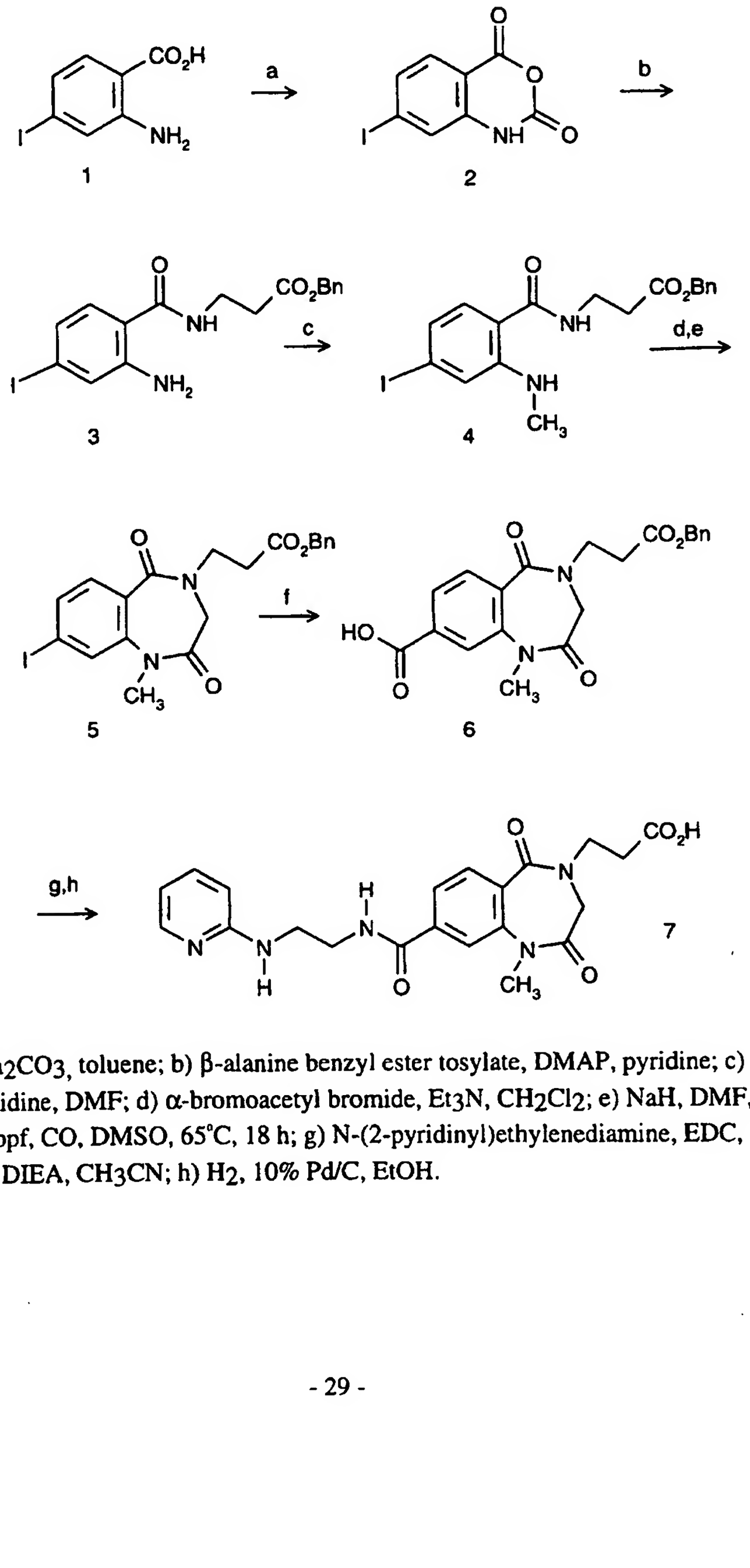
Compounds wherein V is $CH_2CHOH$ may be obtained from a suitably protected compound where V is CH=CH by hydroboration and basic oxidation as disclosed in *Tet. Lett.*, 31, 231 (1990).

The core 6-7 fused ring fibrinogen template of formula (II) is prepared by methods well known in the art, *e.g.*, Hynes, *et al.*, *J. Het. Chem.*, 1988, 25, 1173; Muller, *et al.*, *Helv. Chim. Acta.*, 1982, 65, 2118; Mori, *et al.*, *Heterocycles*, 1981, 16, 1491. Similarly, methods for preparing benzazepines, 1,4-benzothiazepines, 1,4-benzoxazepines and 1,4-benzodiazepines are known and are disclosed, for instance, in Bondinell, *et al.*, International Patent Application WO 93/00095.

Representative fibrinogen antagonist templates may be prepared according to Schemes A - CC, which follow:

Scheme A describes a method of preparing exemplary fibrinogen receptor templates described in Blackburn, *et. al.*, WO 93/08174.

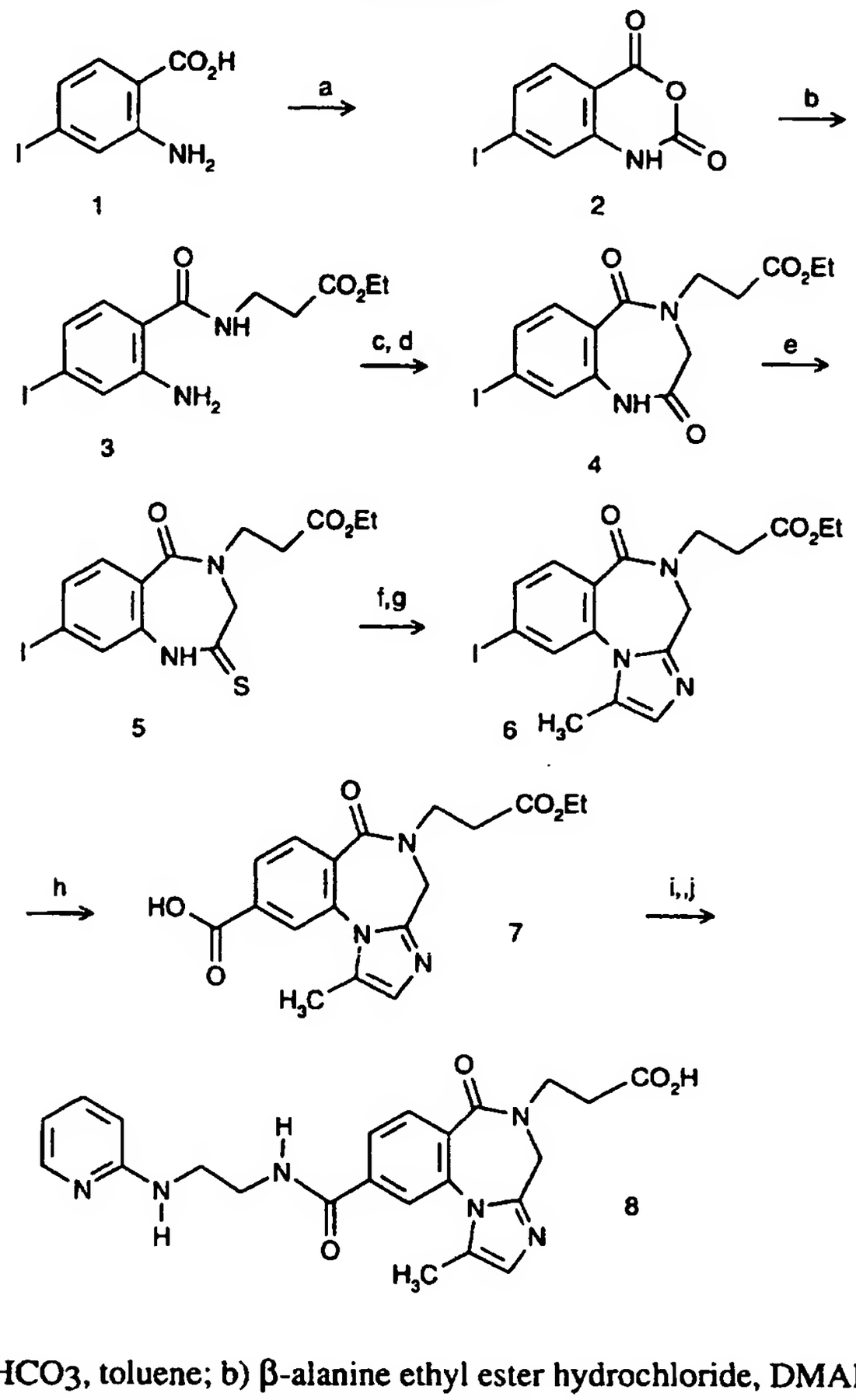
**Scheme A**




a) $COCl_2$, $Na_2CO_3$, toluene; b) β-alanine benzyl ester tosylate, DMAP, pyridine; c) $CH_3I$, 2,6-lutidine, DMF; d) α-bromoacetyl bromide, $Et_3N$, $CH_2Cl_2$; e) NaH, DMF, f) $Pd(OAc)_2$, dppf, CO, DMSO, 65°C, 18 h; g) N-(2-pyridinyl)ethylenediamine, EDC, HOBT·$H_2O$, DIEA, $CH_3CN$; h) $H_2$, 10% Pd/C, EtOH.

Scheme B describes a method of preparing exemplary fibrinogen receptor templates described in Blackburn, *et. al.*, WO 95/04057.

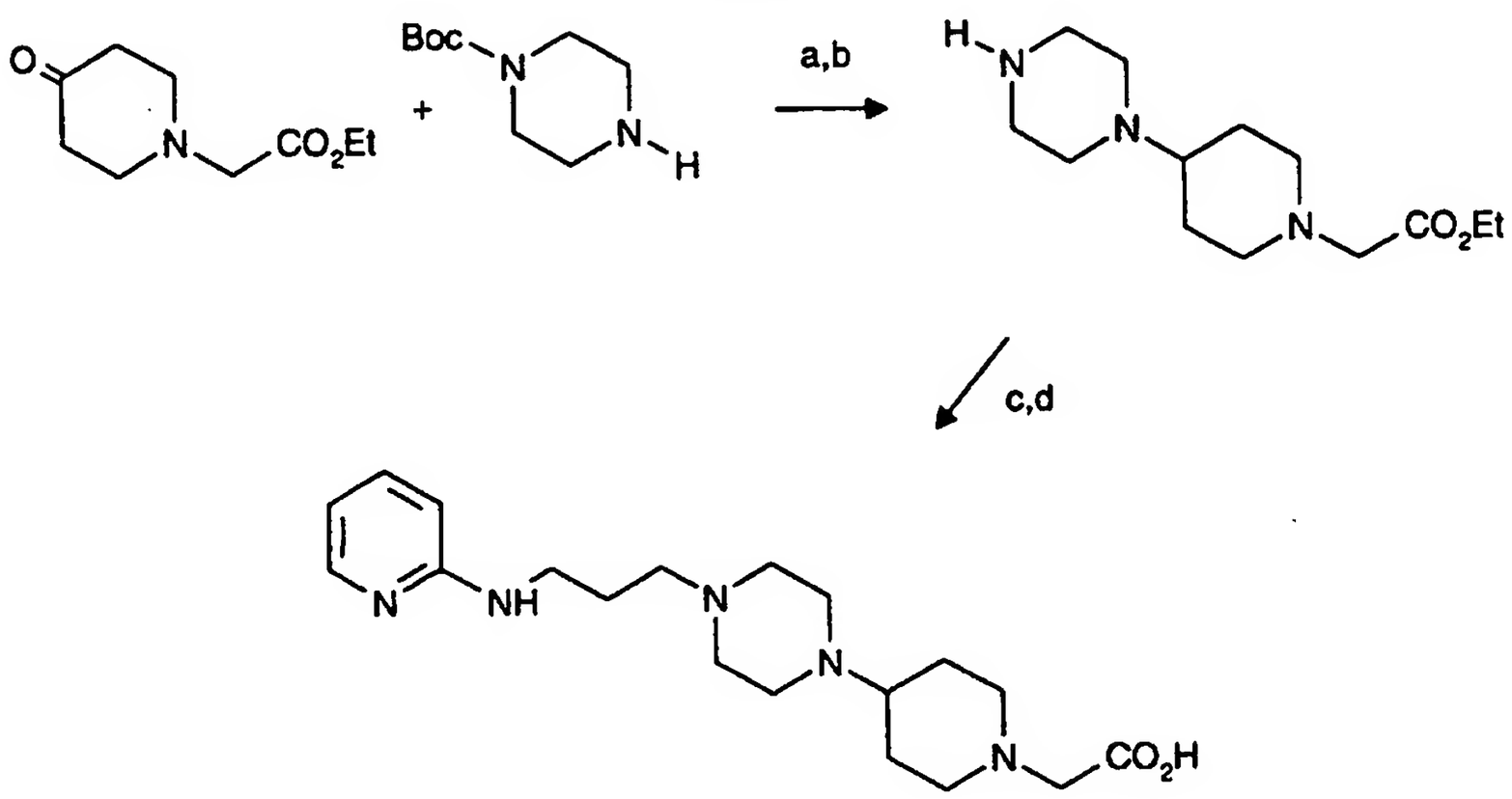
**Scheme B**




a) $COCl_2$, $NaHCO_3$, toluene; b) β-alanine ethyl ester hydrochloride, DMAP, pyridine; c) α-bromoacetyl bromide, $Et_3N$, $CH_2Cl_2$; d) NaH, DMF; e) Lawesson's reagent, THF, 50°C, 2 h; f) $CH_3I$, NaOH, $(n\text{-}Bu)_4N.HSO_4$, $CH_2Cl_2/H_2O$, RT, 2 h; g) propargyl amine, toluene, pyridine hydrochloride, reflux, 6 h; h) $Pd(OAc)_2$, dppf, CO, DMSO, 65°C, 18 h; i) N-(2-pyridinyl)ethylenediamine, EDC, $HOBT{\cdot}H_2O$, DIEA, $CH_3CN$; j) LiOH, $H_2O$, THF, 18 h.

Scheme C describes a method of preparing exemplary fibrinogen receptor templates described in Porter, *et al.*, EP 0542363.

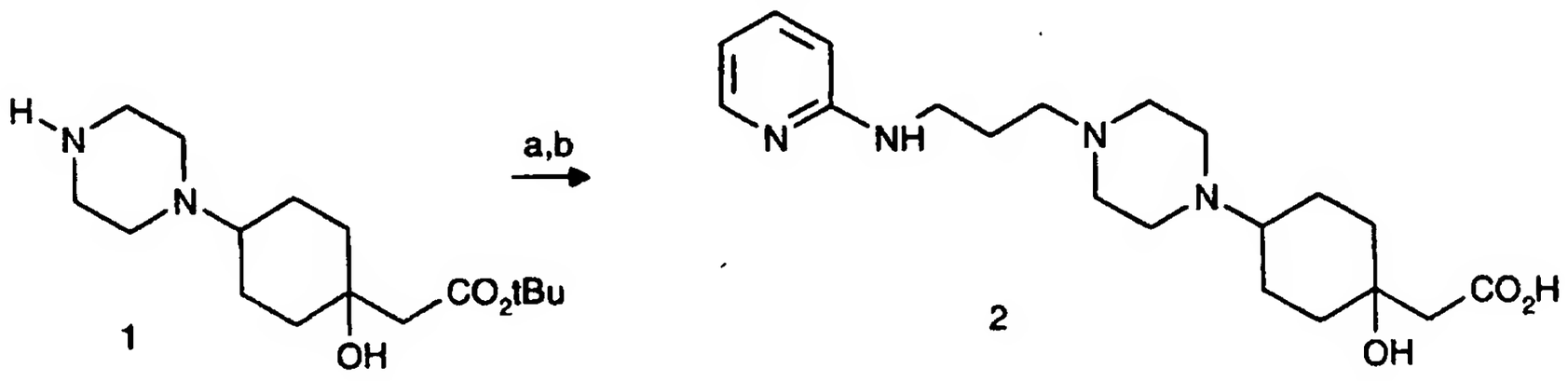
**Scheme C**




a) $NaBH_3CN$, HCl, $CH_3OH$; b) HCl, dioxane, $CH_2Cl_2$; c) 1-chloro-3-[(2-pyridinyl)amino]propane, DIEA, THF; d) NaOH, $H_2O$, $CH_3OH$.

Scheme D describes a method of preparing exemplary fibrinogen receptor templates described in Porter, *et al.*, EP 0537980.

**Scheme D**

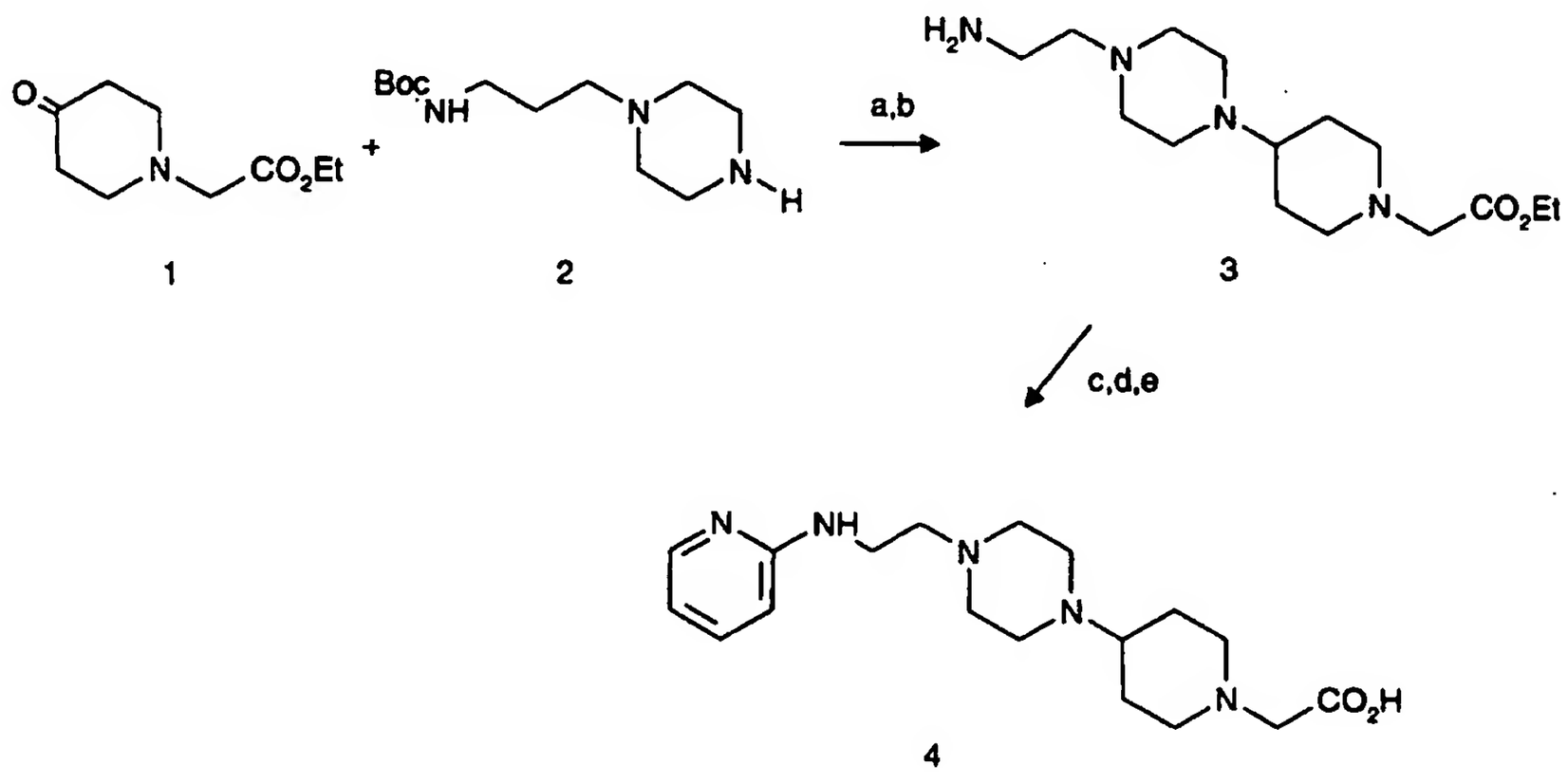



a) 1-chloro-3-[(2-pyridinyl)amino]propane, DIEA, THF; b) NaOH, $H_2O$, $CH_3OH$.

**D-1** is alkylated with 1-chloro-3-[(2-pyridinyl)amino]propane with DIEA in THF, the resulting ester is saponified with NaOH in aqueous $CH_3OH$ to give **D-2**. Alternatively, the tert-butyl ester can be cleaved with TFA or HCl in a suitable solvent such as $CH_2Cl_2$ or dioxane.

Scheme E describes a method of preparing exemplary fibrinogen receptor templates described in Porter, *et al.*, EP 0542363.

**Scheme E**

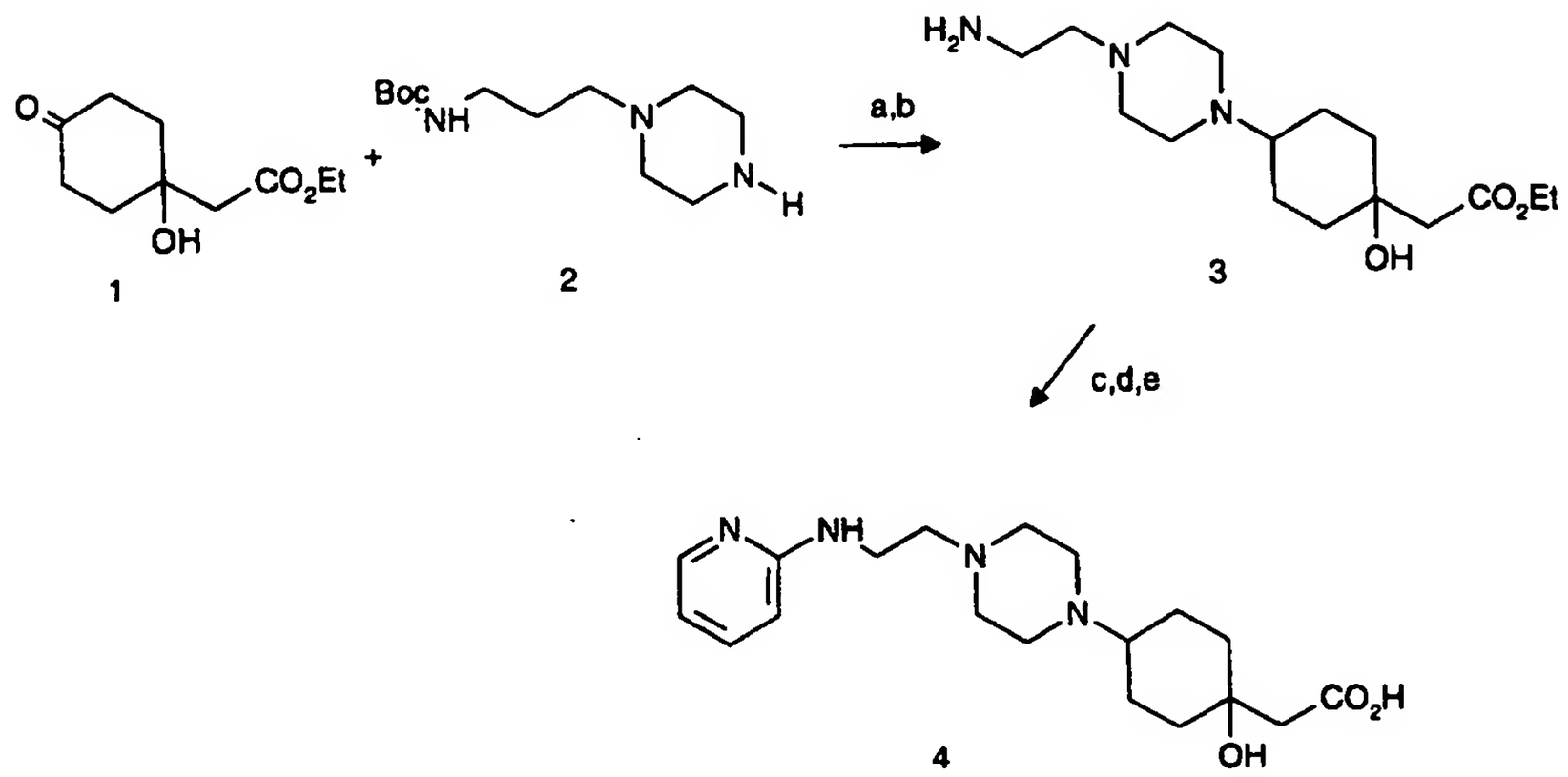



a) $NaBH_3CN$, HCl, $CH_3OH$, EtOH, molecular sieves; b) TFA, $CH_2Cl_2$; c) 2-chloropyridine-N-oxide, $NaHCO_3$, butanol; d) $HCO_2K$, 10% Pd/C, $CH_3OH$; e) 1N NaOH, $CH_3OH$.

Reductive amination of **E-1** with **E-2** using NaBH3CN, HCl, and molecular sieves in $CH_3OH$ and EtOH, followed by treatment of the product with TFA in $CH_2Cl_2$ gives **E-3**. Treatment of E-3 with 2-chloropyridine-N-oxide and $NaHCO_3$ in butanol with heating, followed by reduction of the N-oxide with $HCO_2K$ and 10% Pd/C in $CH_3OH$, and saponification of the ethyl ester with 1N NaOH in $CH_3OH$ gives **E-4**.

Scheme F describes a method of preparing exemplary fibrinogen receptor templates described in Porter, *et al.*, EP 0537980.

**Scheme F**

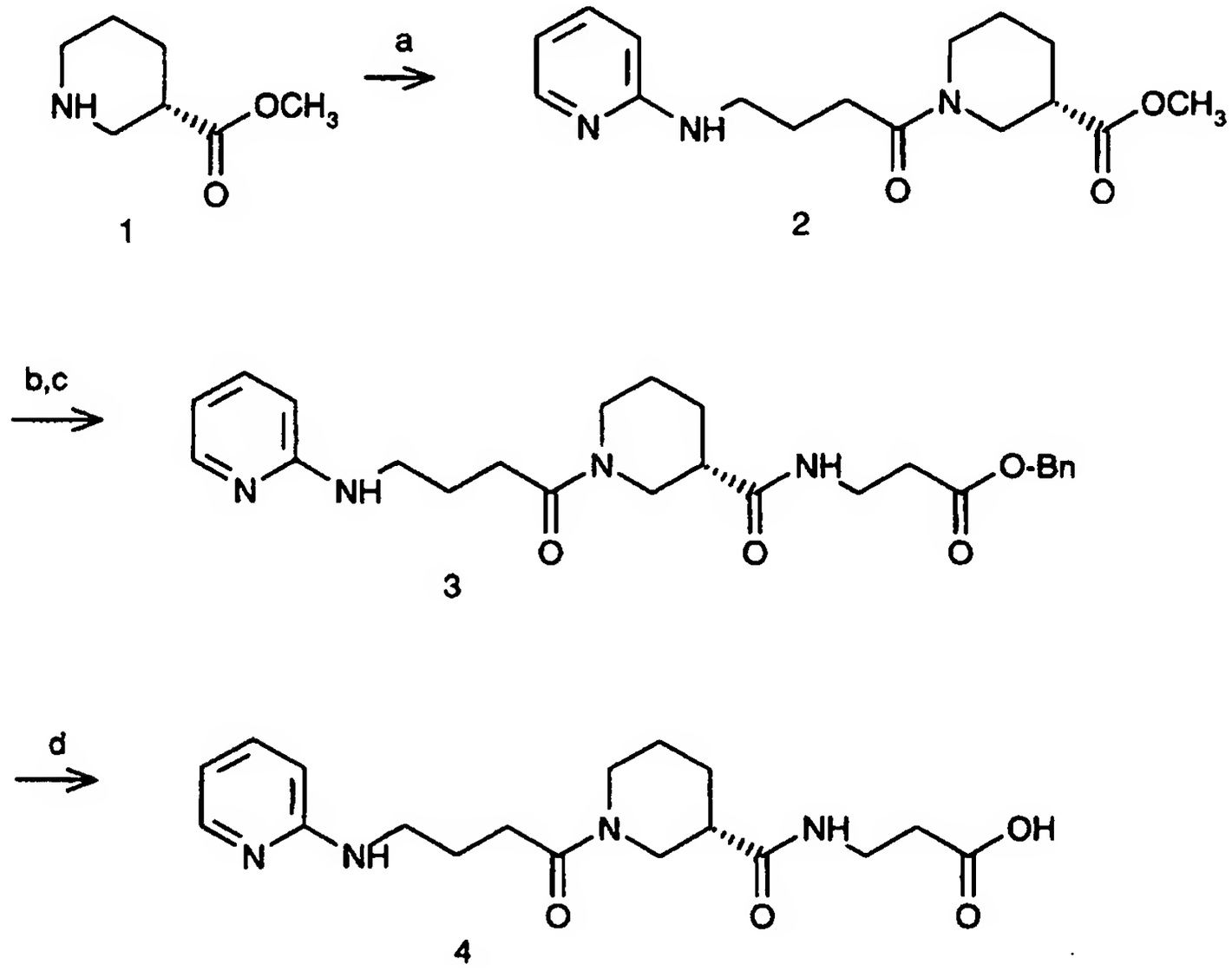



a) $NaBH_3CN$, HCl, $CH_3OH$, EtOH, molecular sieves; b) TFA, $CH_2Cl_2$; c) 2-chloropyridine-N-oxide, $NaHCO_3$, butanol; d) $HCO_2K$, 10% Pd/C, $CH_3OH$; e) 1N NaOH, $CH_3OH$.

Reductive amination of **F-1** with **F-2** using NaBH3CN, HCl, and molecular sieves in $CH_3OH$ and EtOH, followed by treatment of the product with TFA in $CH_2Cl_2$ gives **F-3**. Treatment of E-3 with 2-chloropyridine-N-oxide and $NaHCO_3$ in butanol with heating, followed by reduction of the N-oxide with $HCO_2K$ and 10% Pd/C in $CH_3OH$, and saponification of the ethyl ester with 1N NaOH in $CH_3OH$ gives **F-4**.

Scheme G describes a method of preparing exemplary fibrinogen receptor templates described in Beavers, *et al.*, WO 95/25091.

**Scheme G**




5

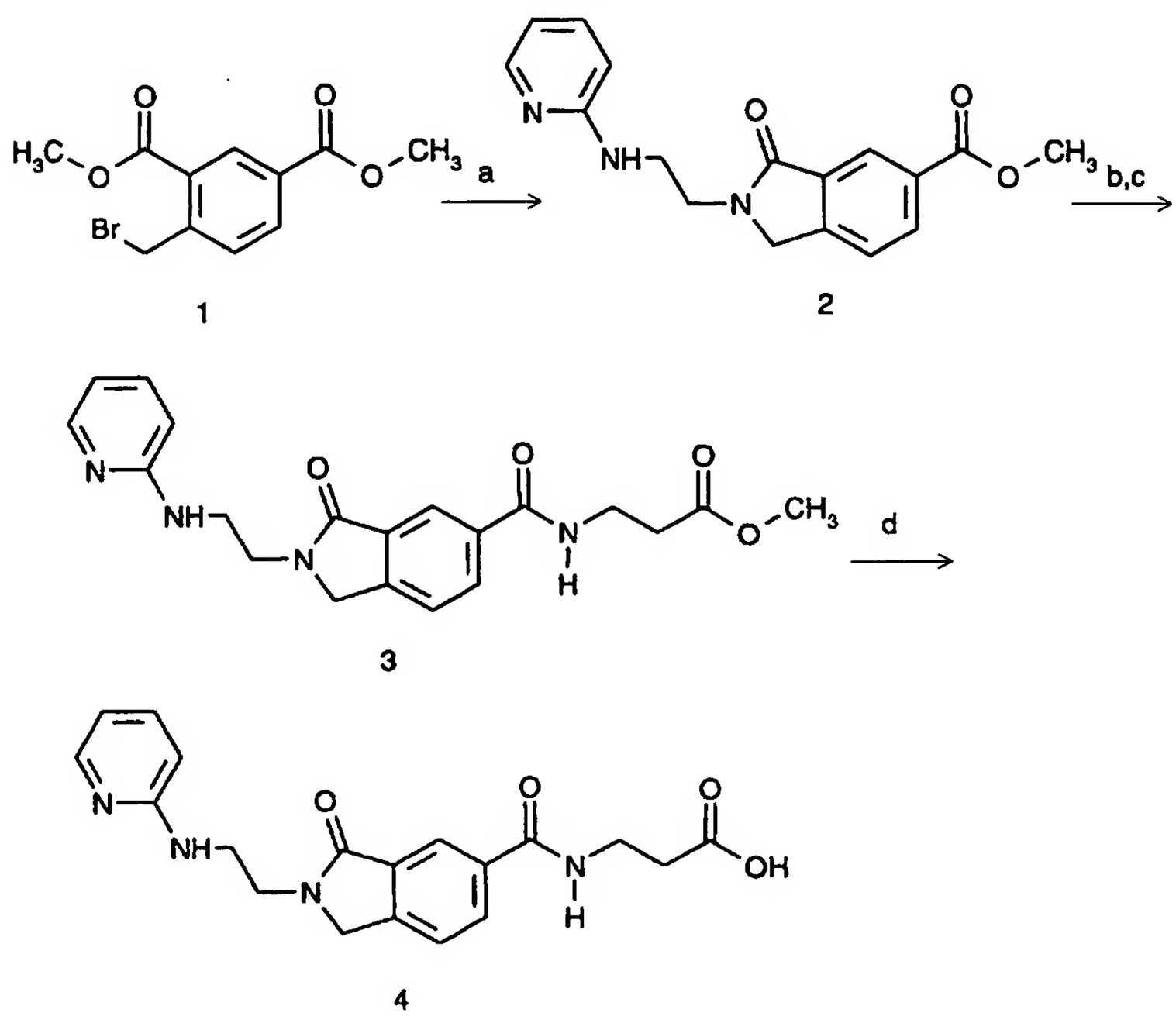
a) N-[2-(pyridinyl)amino]butyric acid, BOP-Cl, NMM, $CH_2Cl_2$; b) LiOH, $H_2O$, THF; c) β-alanine benzyl ester, EDC, HOBT, NMM, $CH_2Cl_2$; d) $H_2$, 10% Pd/C, AcOH, THF, $H_2O$.

10

Following the procedures of Beavers, *et al.*, WO 95/25091, Example 1, except substituting N-[2-(pyridinyl)amino]butyric acid, for $N^{\alpha}$-Boc-D-lys(Cbz)-OH, gives **F-4**.

Scheme H describes a method of preparing exemplary fibrinogen receptor templates described in Hartman, *et al.*, EP 0540334.

**Scheme H**



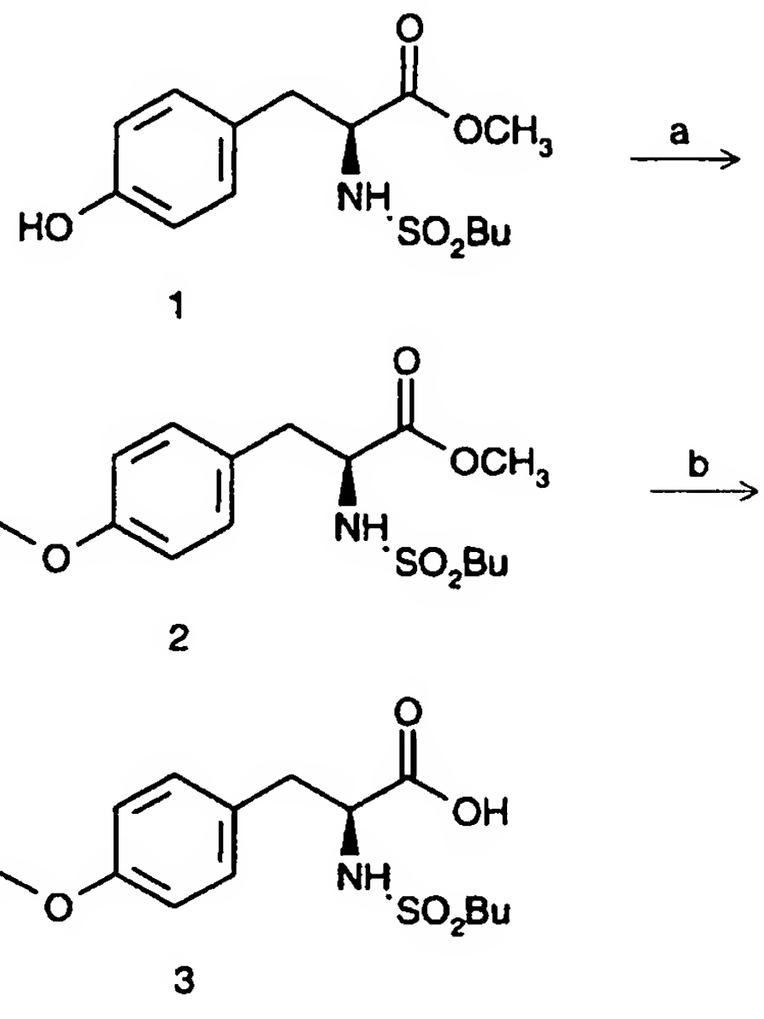

5

a) N-(2-pyridinyl)ethylenediamine, $Et_3N$, benzene; b) 1.0 N LiOH, $H_2O$, $CH_3OH$; c) β-alanine ethyl ester, BOP, $Et_3N$, $CH_3CN$; d) LiOH, $H_2O$, THF, $CH_3OH$.

10 Dimethyl 4-(bromomethyl)benzene-1,3-dicarboxylate, **H-1**, is treated with a suitably functionalized amine, such as N-(2-pyridinyl)ethylenediamine, under the general conditions described for 2,3-dihydro-N-(2-carboxy-ethyl)-2-[2-(piperidinyl)ethyl]-3-oxo-1H-isoindole-5-carboxamide in Hartman, *et al.*, EP 0540334, to give **H-4**.

Scheme I describes a method of preparing exemplary fibrinogen receptor templates described in Egbertson, *et al.*, EP 0478363.

**Scheme I**

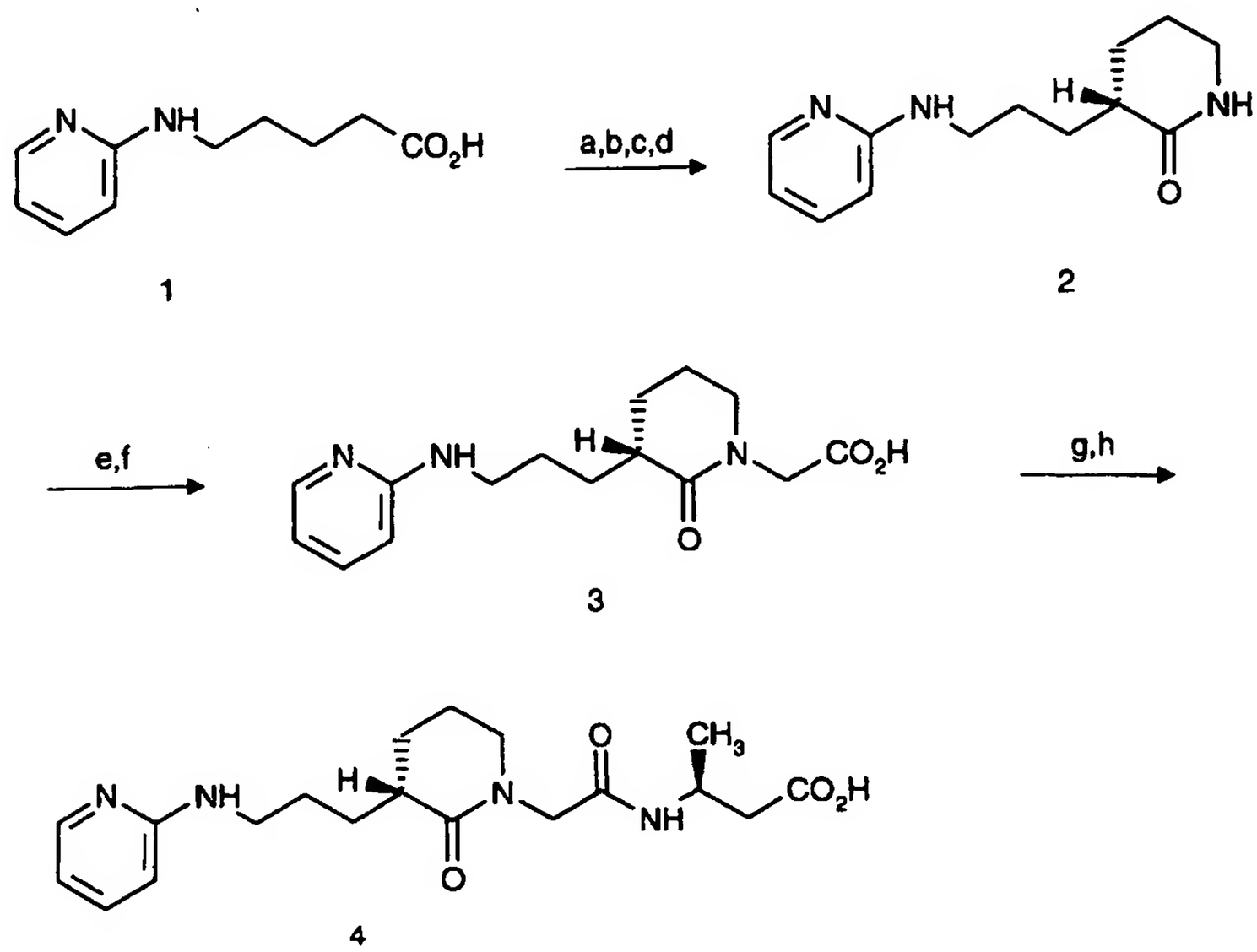



a) 4-[(2-pyridinyl)amino]butanol, $Ph_3P$, DEAD, $CH_2Cl_2$, benzene; b) 1.0 N LiOH, THF, $H_2O$.

N-(n-Butylsulfonyl)-L-tyrosine methyl ester, **I-1**, is treated with a suitably functionalized alcohol, such as 4-[(2-pyridinyl)amino]butanol, to give **I-3**.

Scheme J describes a method of preparing exemplary fibrinogen receptor templates described in Duggan, *et al.*, *J. Med. Chem.* **1995**, *38*, 3332.

**Scheme J**



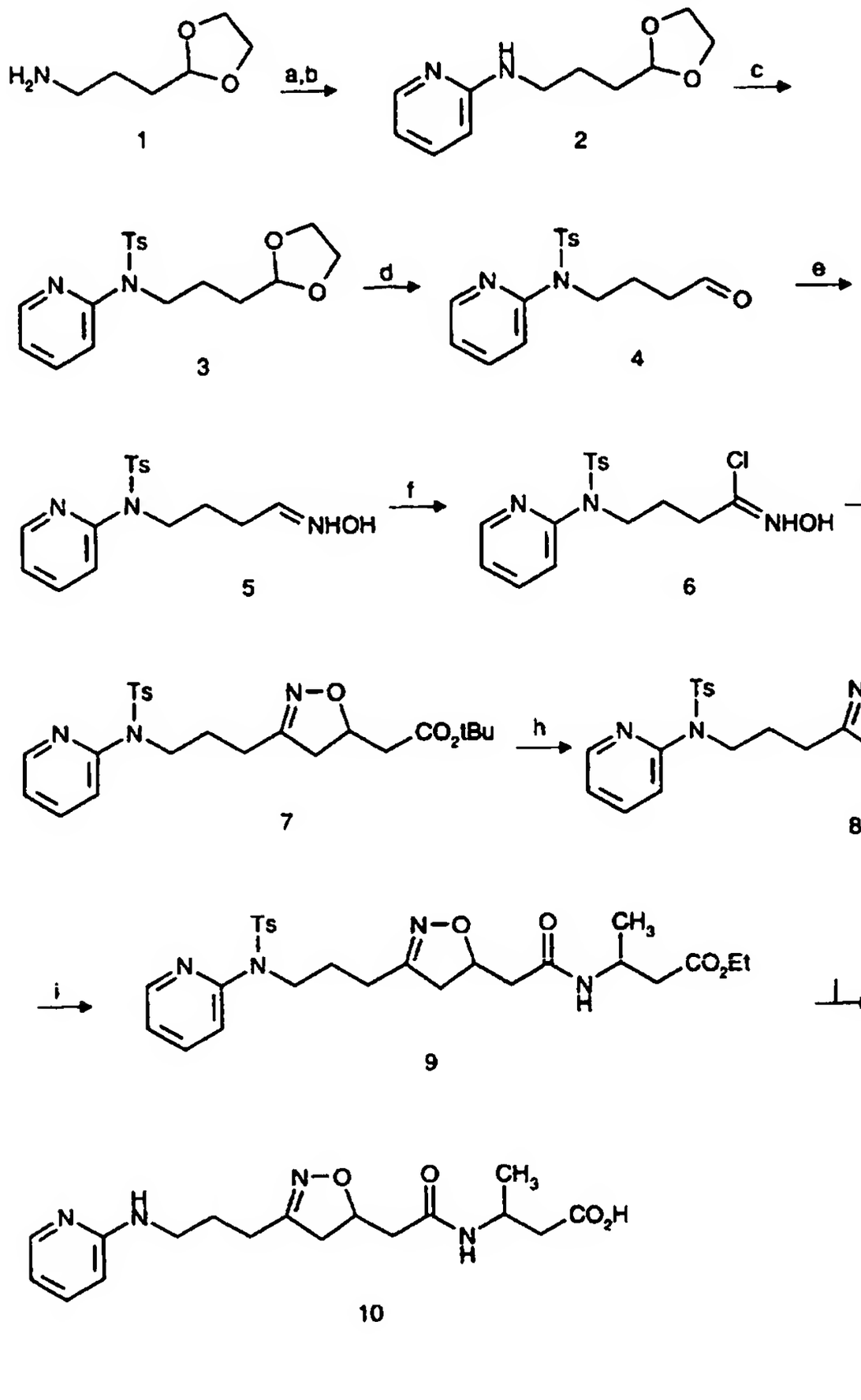

a) pivaloyl chloride, $Et_3N$, THF, (S)-4-benzyl-2-oxazolidinone; b) $Ti(O\text{-}i\text{-}Pr)Cl_2$, acrylonitrile, DIEA, $CH_2Cl_2$; c) $H_2$, $PtO_2$, $CH_3OH$, $CHCl_3$; d) $NaHCO_3$, $CH_3CN$; e) NaHMDS, ethyl bromoacetate; f) 1 N NaOH, $CH_3OH$; g) 3(R)-methyl-β-alanine ethyl ester HCl , EDC, HOBT, $Et_3N$, DMF; h) 1 N NaOH, $CH_3OH$.

A suitably functionalized carboxylic acid, such as 5-[(pyrid-2-yl)amino]pentanoic acid, **J-1**, is activated and reacted with a chiral auxiliary such as lithium (S)-4-benzyl-2-oxazolidinone to form a chiral Evans reagent. Alkylation of the titanium enolate with acrylonitrile, followed by nitrile reduction and lactam formation affords lactam **J-2**. Alkylation of the lactam with agents such as ethyl bromoacetate followed by ester saponification yields the carboxylic acid **J-3**. The resulting carboxylic acid derivative **J-3** is converted to an activated form of the carboxylic acid using, for example, EDC and HOBt, or $SOCl_2$, and the activated form is subsequently reacted with an appropriate

amine, for instance the 3(R)-methyl-β-alanine ethyl ester, in a suitable solvent such as DMF, $CH_2Cl_2$, or $CH_3CN$. Depending on whether acid neutralization is required, an added base, such as DIEA or pyridine, may be used. Many additional methods for converting a carboxylic acid to an amide are known, and can be found in standard reference books, such as "Compendium of Organic Synthetic Methods", Vol. I - VI (published by Wiley-Interscience), or Bodansky, "The Practice of Peptide Synthesis" (published by Springer-Verlag). Hydrolysis of the ethyl ester is accomplished according to the general conditions described for the conversion of **J-2** to **J-3**, to provide the carboxylic acid **J-4**. Alternatively, the intermediate carboxylate salt of can be isolated, if desired, or a carboxylate salt of the free carboxylic acid can be prepared by methods well-known to those of skill in the art.

Scheme K describes a method of preparing exemplary fibrinogen receptor templates described in WO 93/07867.

**Scheme K**



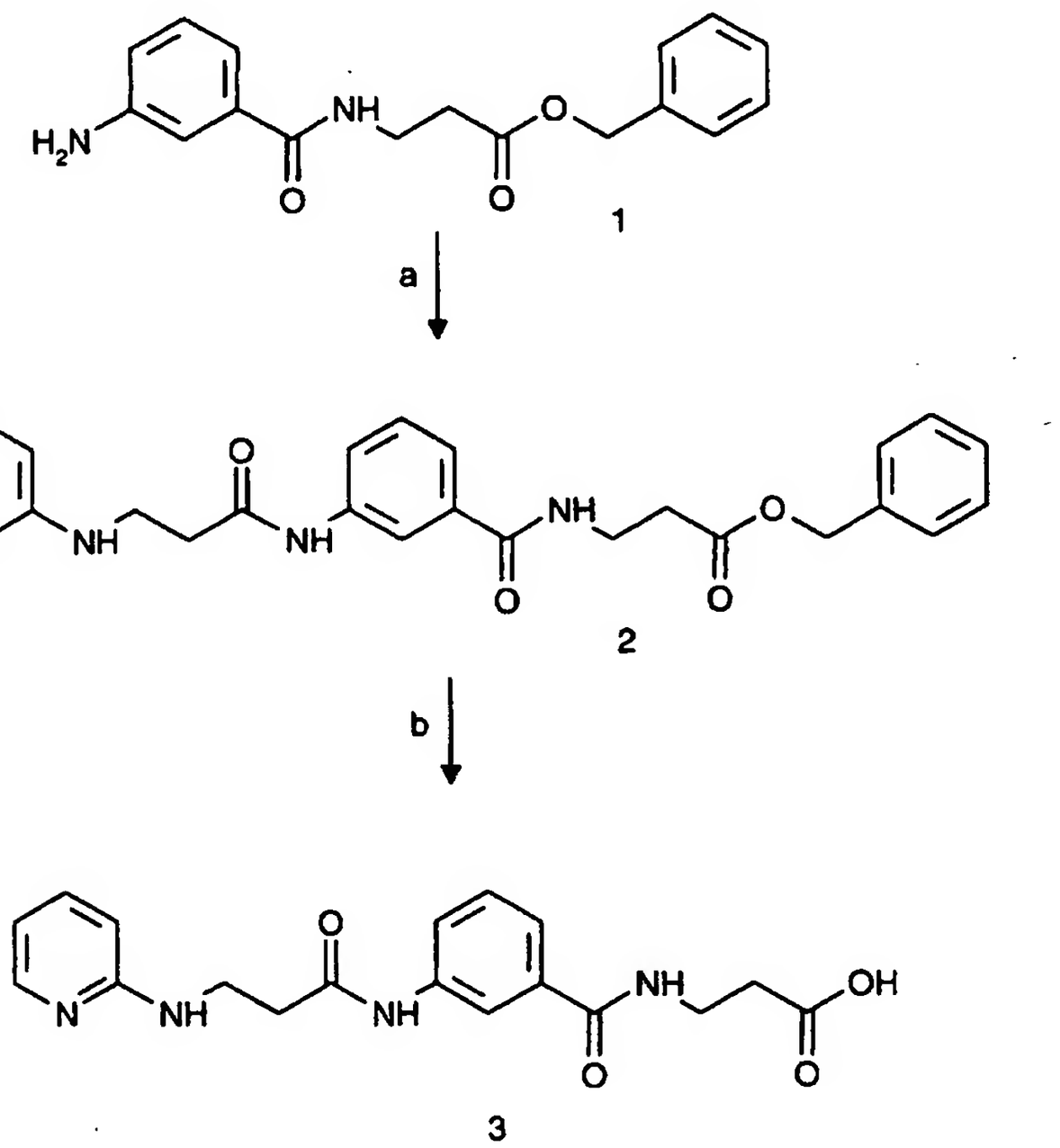

a) 2-chloropyridine N-oxide hydrochloride, $NaHCO_3$, tert-amyl alcohol; b) $HCO_2NH_4$, Pd/C, EtOH; c) TsCl, NaH, THF; d) p-TsOH·$H_2O$, acetone, $H_2O$; e) $NH_2OH$·HCl, NaOAc, $CH_3OH$; f) NCS, DMF; g) tert-butyl 3-butenoate, $Et_3N$; h) 4M HCl, dioxane, $CH_2Cl_2$; i) ethyl 3-aminobutyrate, EDC, HOBt·$H_2O$, DIEA, $CH_3CN$; j) 1.0 N LiOH, THF, $H_2O$.

Readily available 2-(3-aminopropyl)-1,3-dioxolane, **K-1**, *Chem. Pharm. Bull.* **1982**, *30*, 909-914, is converted to the pyridyl derivative **K-2** according to the general protocol described by Misra, *Bioorg. Med. Chem. Lett.* **1994**, *4*, 2165-2170. Protection of one of the nitrogen atoms of the aminopyridine moiety in **K-2** can be accomplished by reaction with a sulfonyl chloride, for instance p-toluenesulfonyl chloride, in the presence of a suitable base, generally NaH or an aqueous alkali metal hydroxide, in an inert solvent, preferably THF, to afford **K-3**. Alternative protecting groups known to those of skill in the art may be used, as long as they are compatible with the subsequent chemistry and can be removed when desired. Such protecting groups are described in Greene, "Protective Groups in Organic Synthesis" (published by Wiley-Interscience). Removal of the dioxolanyl protecting group of **K-3** to afford the aldehyde **K-4** can be conveniently accomplished under mild acidic conditions, such as p-toluenesulfonic acid, in an appropriate solvent, preferably aqueous acetone. The aldehyde is converted to the aldoxime **K-5** by standard procedures known to those of skill in the art, and this aldoxime is oxidized to the oximinoyl chloride derivative **K-6** by the methods described in WO 95/14682 and WO 95/14683. Reaction of **K-6** with an olefin, such as tert-butyl 3-butenoate (*Tet. Lett.* **1985**, *26*, 381-384), in the presence of a suitable base, for instance $Et_3N$ or DIEA, in an inert solvent such as benzene or toluene, according to the protocol described in WO 95/14682 and WO 95/14683, gives the cycloadduct **K-7**. The tert-butyl ester of **K-7** is removed under standard acidic conditions, generally TFA in $CH_2Cl_2$ or HCl in dioxane, to give the carboxylic acid **K-8**. The carboxylic acid is activated using, for example, EDC and HOBt, or $SOCl_2$, and the activated form is subsequently reacted with an appropriate amine, for instance a suitable derivative of β-alanine, in a neutral solvent, such as DMF, $CH_2Cl_2$, or $CH_3CN$, to afford **K-9**. Depending on whether acid neutralization is required, an added base, such as DIEA or pyridine, may be used. Many additional methods for converting a carboxylic acid to an amide are known, and can be found in standard reference books, such as "Compendium of Organic Synthetic Methods", Vol. I - VI (published by Wiley-Interscience), or Bodansky, "The Practice of Peptide Synthesis" (published by Springer-Verlag). Derivatives of β–alanine are readily available in either racemic or optically pure form by a variety of methods known to those of skill in

the art. A representative method is described in WO 93/07867. The ethyl ester and sulfonyl protecting groups of **K-9** are removed using aqueous base, for example, LiOH in aqueous THF or NaOH in aqueous $CH_3OH$ or EtOH. The intermediate carboxylate salt is acidified with a suitable acid, for instance TFA or HCl, to afford the carboxylic acid **K-10**. Alternatively, the intermediate carboxylate salt can be isolated, if desired, or a carboxylate salt of the free carboxylic acid can be prepared by methods well-known to those of skill in the art.

Scheme L describes a method of preparing exemplary fibrinogen receptor templates described in Alig, *et al.*, EP 0372486.

**Scheme L**

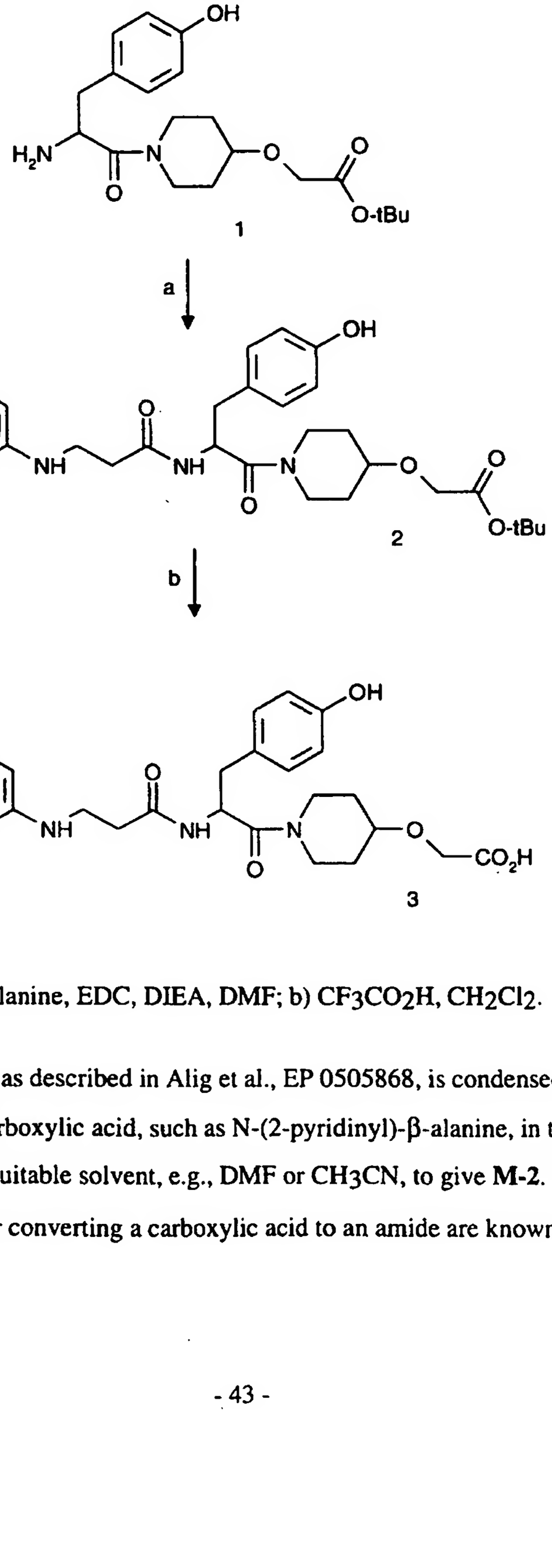



a) N-(2-pyridinyl)-β-alanine, EDC, DIEA, DMF; b) NaOH, $H_2O$, $CH_3OH$.

**L-1**, prepared as described in Alig *et al.*, EP 0372486, is condensed with a suitable substituted carboxylic acid, such as N-(2-pyridinyl)-β-alanine, in the presence of EDC and DIEA, and in a suitable solvent, e.g., DMF or $CH_3CN$, to give **L-2**. Many additional methods for converting a carboxylic acid to an amide are known, and can be found in standard reference books, such a "Compendium of Organic Synthesis", Vol. I-VI (published by Springer-Verlag). Hydrolysis of the ester in **L-2** is accomplished by saponification with a suitable reagent, e.g., NaOH, in a suitable solvent, e.g., aqueous $CH_3OH$. Alternatively, the benzyl ester in **L-2** may be converted to the acid by treatment with hydrogen and a suitable catalyst, e.g., Pd/C, in a suitable solvent, e.g., $CH_3OH$, EtOH, or AcOH.

Scheme M describes a method of preparing exemplary fibrinogen receptor templates described in Alig, *et al.*, EP 0505868.

**Scheme M**



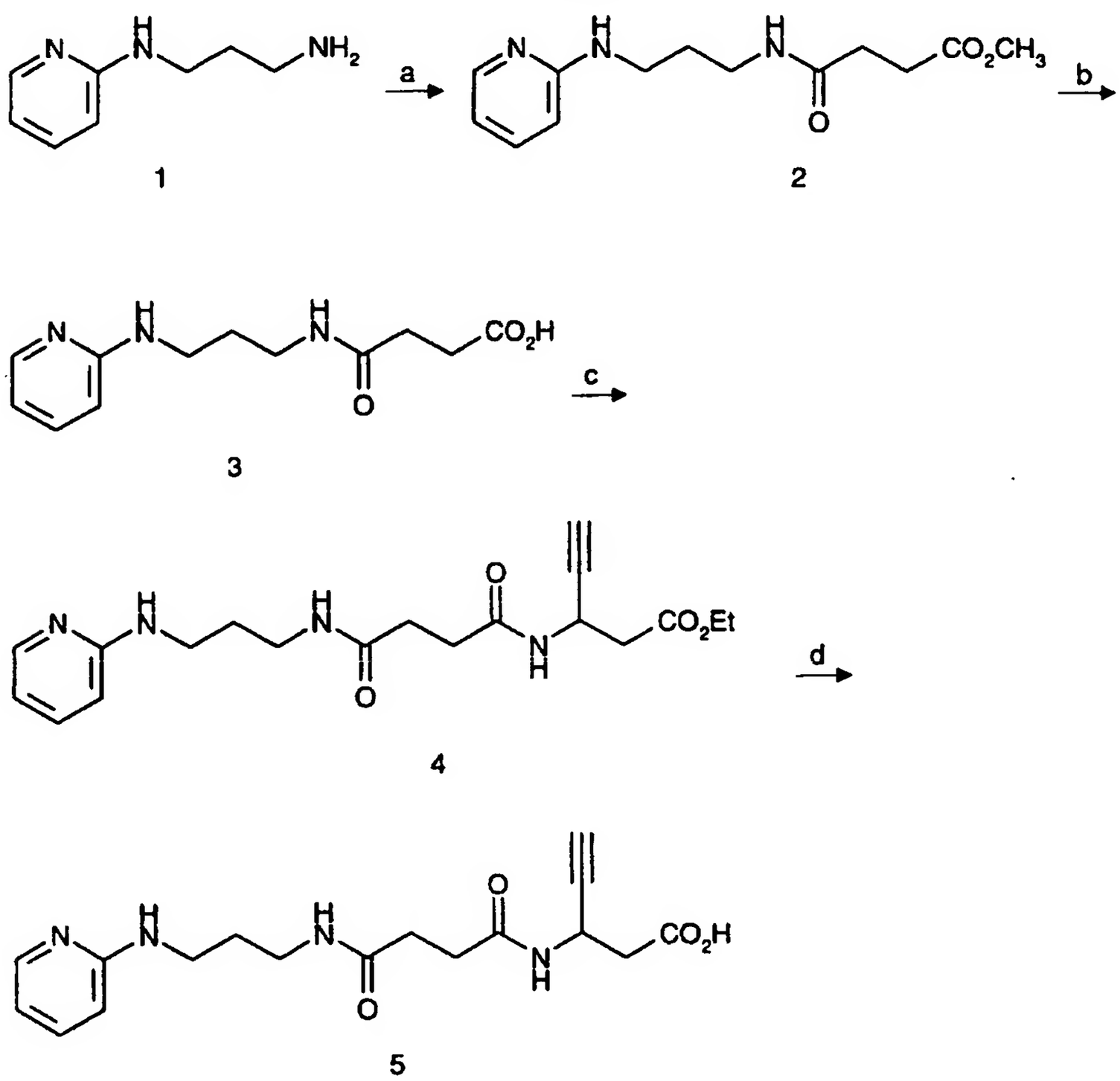

a) N-(2-pyridinyl)-β-alanine, EDC, DIEA, DMF; b) $CF_3CO_2H$, $CH_2Cl_2$.

**M-1**, prepared as described in Alig et al., EP 0505868, is condensed with a suitable substituted carboxylic acid, such as N-(2-pyridinyl)-β-alanine, in the presence of EDC and DIEA, in a suitable solvent, e.g., DMF or $CH_3CN$, to give **M-2**. Many additional methods for converting a carboxylic acid to an amide are known, and can be

found in standard reference books, such as "Compendium of Organic Synthesis", Vol. I-VI (published by Springer-Verlag). Hydrolysis of the ester in **M-2** is accomplished with trifluoroacetic acid or hydrogen chloride to give **M-3**. Alternatively, the ester in **M-2** may be saponified with a suitable reagent, e.g., 1N NaOH, in a suitable solvent, e.g., $CH_3OH$.

Scheme N describes a method of preparing exemplary fibrinogen receptor templates described in WO 93/07867.

**Scheme N**

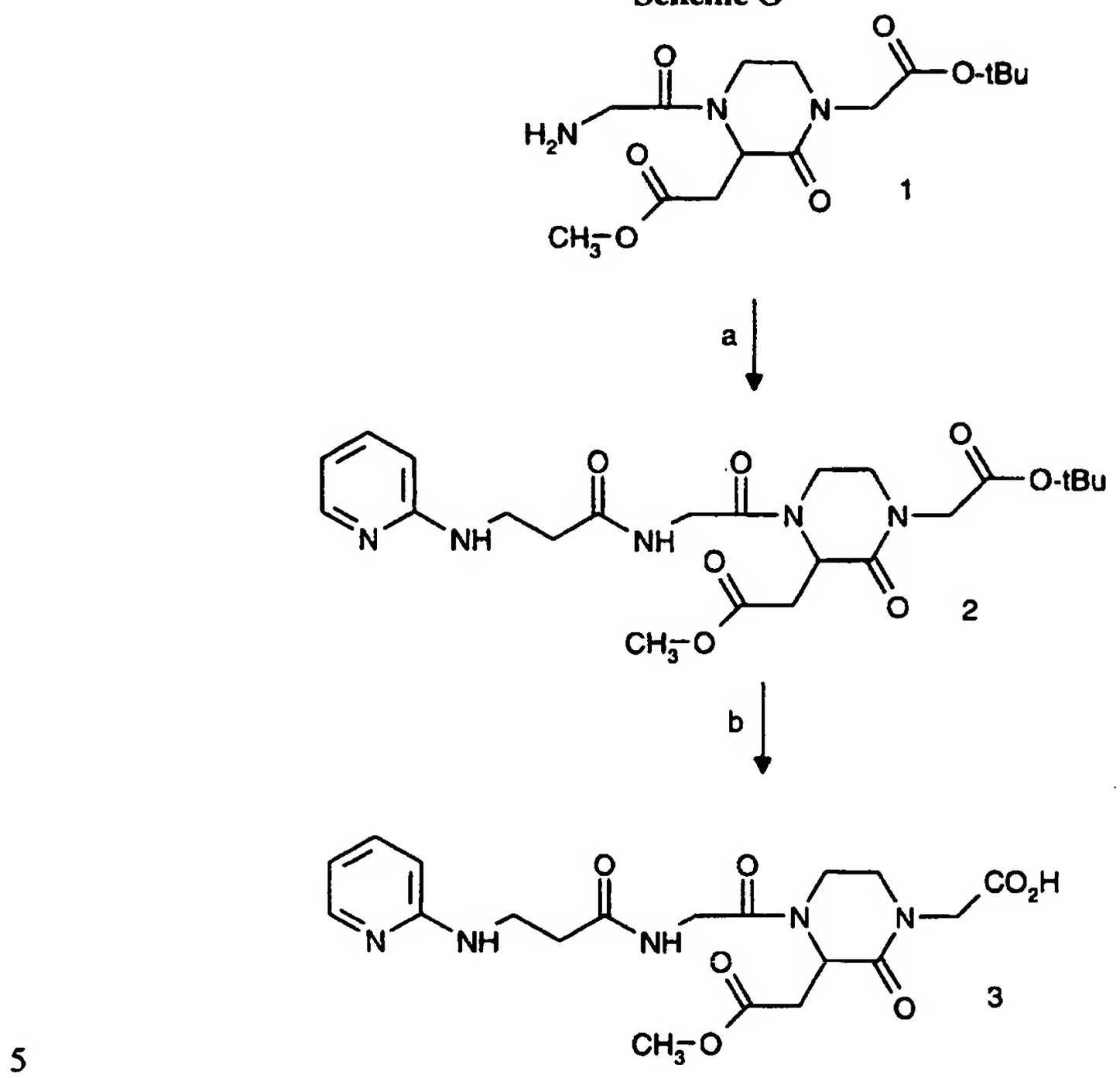



a) 3-(carbomethoxy)propionyl chloride, DIEA, $CH_2Cl_2$; b) 1.0 N NaOH, $CH_3OH$; c) ethyl 3-amino-4-pentynoate, EDC, HOBt·$H_2O$, DIEA, $CH_3CN$; d) 1.0 N LiOH, THF, $H_2O$.

A suitably functionalized amine, such as 2-[(3-aminoprop-1-yl)amino]pyridine, is reacted with 3-(carbomethoxy)propionyl chloride in the presence of an appropriate acid scavenger, such as $Et_3N$, DIEA, or pyridine, in a neutral solvent, generally $CH_2Cl_2$, to afford **N-2**. The methyl ester of **N-2** is hydrolyzed using aqueous base, for example, LiOH in aqueous THF or NaOH in aqueous $CH_3OH$ or EtOH, and the intermediate carboxylate salt is acidified with a suitable acid, for instance TFA or HCl, to afford the carboxylic acid **N-3**. Alternatively, **N-1** can be reacted with succinic anhydride in the presence of an appropriate base, such as $Et_3N$, DIEA, or pyridine, in a neutral solvent, generally $CH_2Cl_2$, to afford **N-3** directly. The resulting carboxylic acid derivative **N-3** is converted to an activated form of the carboxylic acid using, for example, EDC and HOBt, or $SOCl_2$, and the activated form is subsequently reacted with an appropriate amine, for instance the known ethyl 3-amino-4-pentynoate (WO 93/07867), in a suitable solvent such as DMF, $CH_2Cl_2$, or $CH_3CN$, to **N-4**. Depending on whether acid neutralization is required, an added base, such as DIEA or pyridine, may be used. Many additional methods for converting a carboxylic acid to an amide are known, and can be found in standard reference books, such as "Compendium of Organic Synthetic Methods", Vol. I - VI (published by Wiley-Interscience), or Bodansky, "The Practice of Peptide Synthesis" (published by Springer-Verlag). Hydrolysis of the ethyl ester of **N-4** is accomplished according to the general conditions described for the conversion of **N-2** to **N-3**, to provide the carboxylic acid **N-5**. Alternatively, the intermediate carboxylate salt of can be isolated, if desired, or a carboxylate salt of the free carboxylic acid can be prepared by methods well-known to those of skill in the art.

Scheme O describes a method of preparing exemplary fibrinogen receptor templates described in Sugihara, *et al.*, EP 0529858.

**Scheme O**

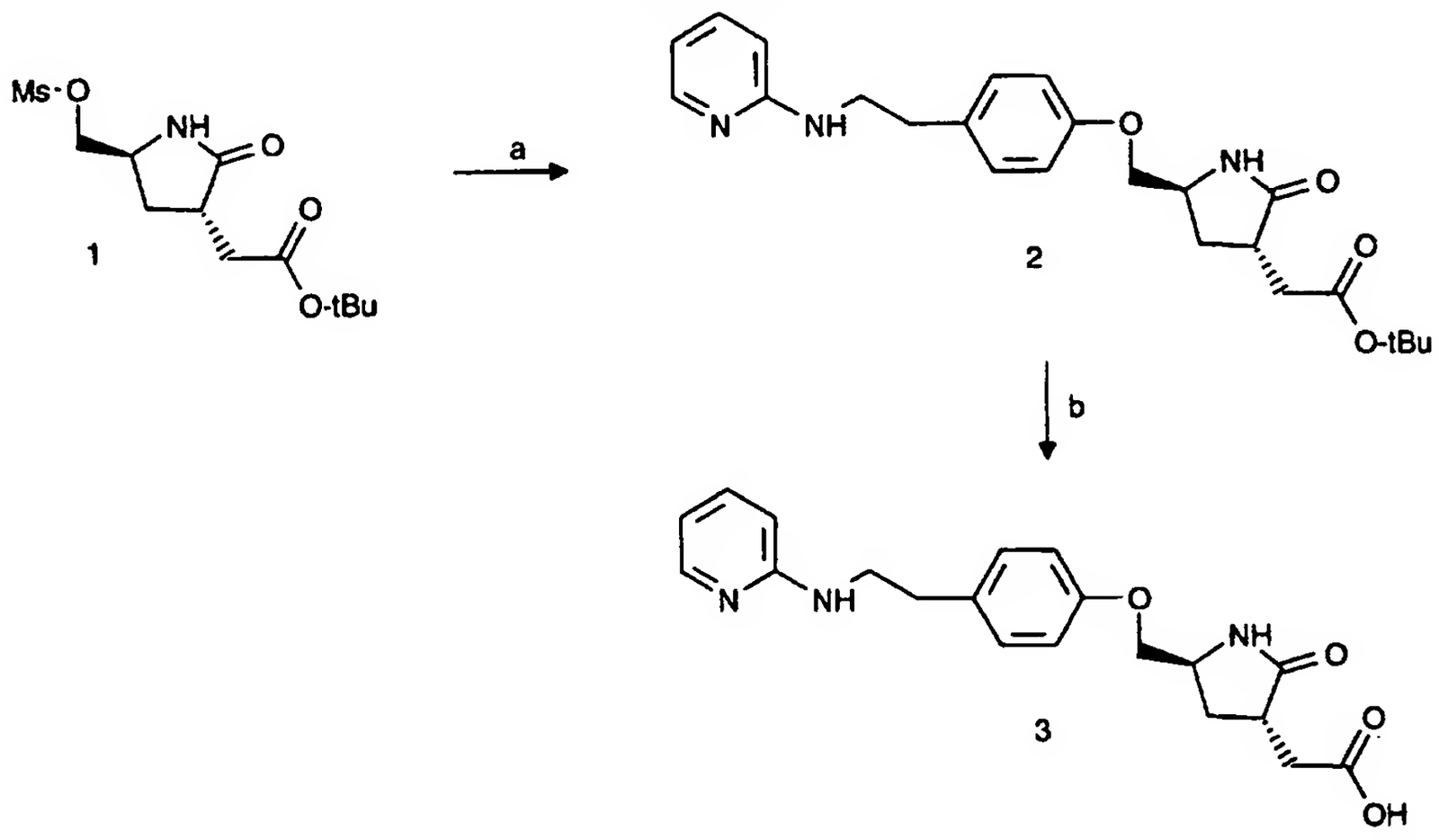



a) N-(2-pyridinyl)-β-alanine, EDC, DIEA, DMF; b) $CF_3CO_2H$, $CH_2Cl_2$.

**O-1**, prepared as described in Sugihara, *et al.*, EP 0529858, is condensed with a suitable substituted carboxylic acid, such N-(2-pyridinyl)-β-alanine, to give **O-2**, and the tert-butyl ester is cleaved with TFA, following the general procedure of Sugihara, et al., Example 59, to give **O-3**. Many additional methods for converting a carboxylic acid to an amide are known, and can be found in standard reference books, such as "Compendium of Organic Synthesis", Vol. I-VI (published by Springer-Verlag).

Scheme P describes a method of preparing exemplary fibrinogen receptor templates described in Himmelsbach, *el. al.*, AU-A-86926/91.

**Scheme P**

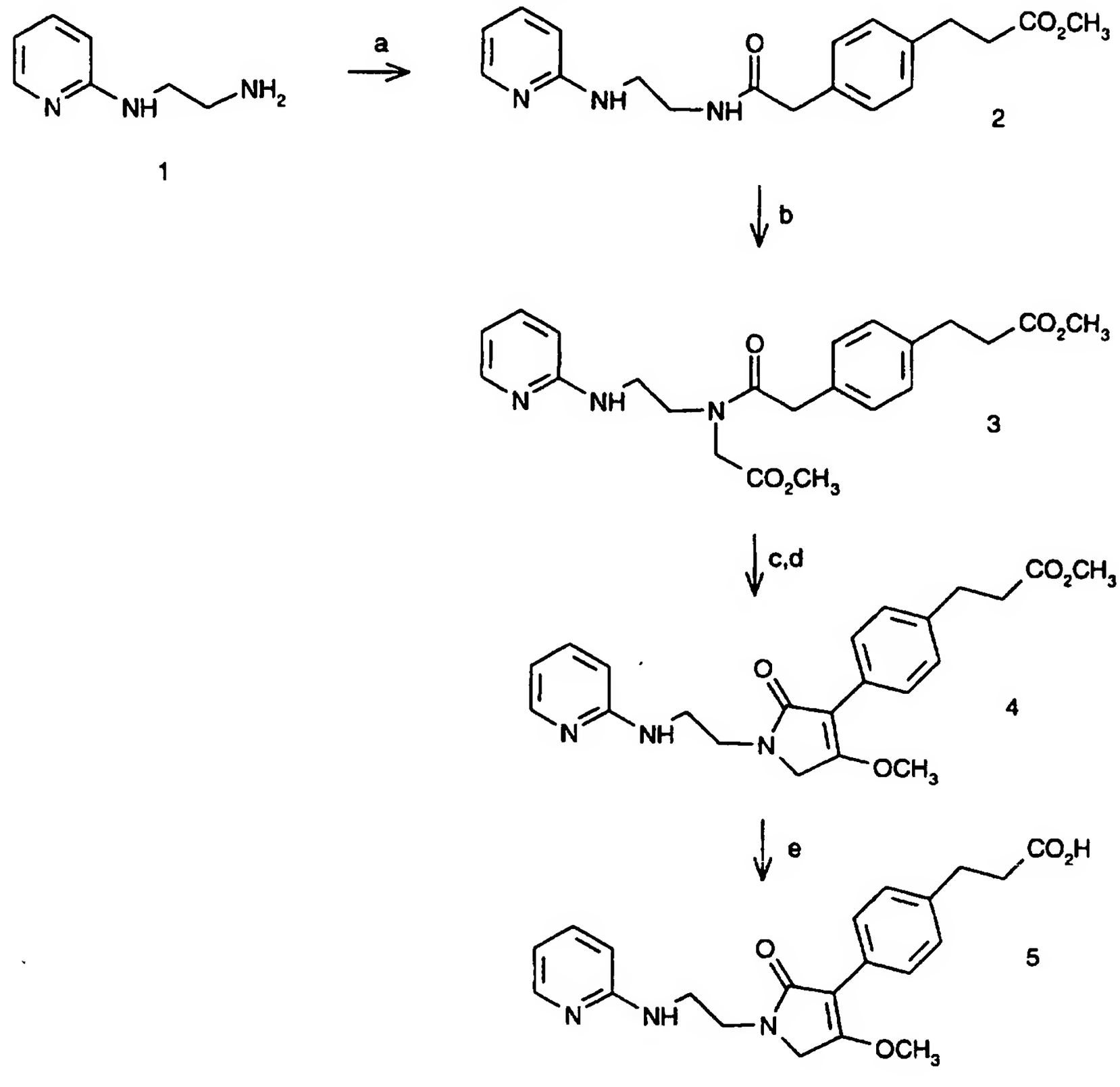



a) 4-[(6-amino-2-pyridinyl)methyl]phenol, $Cs_2CO_3$, DMF; b) 1N NaOH, $CH_3OH$.

Compound **P-1**, prepared as described by Himmelsbach, *et al.*, AU-A-86926/91, Example VI(28), is treated with a suitable substituted phenol, such as 4-[2-[2-(pyridinyl)amino]ethyl]phenol, following the general method of Himmelsbach et al., Example 3(51), to give **P-2**. The tert-butyl ester in **P-2** is hydrolyzed with 1N NaOH in $CH_3OH$ to give **P-3**. Alternatively, the tert-butyl ester may be cleaved with TFA or HCl in a suitable solvent such as $CH_2Cl_2$.

Scheme Q describes a method of preparing exemplary fibrinogen receptor templates described in Linz, *et al.*, EP 0567968.

**Scheme Q**

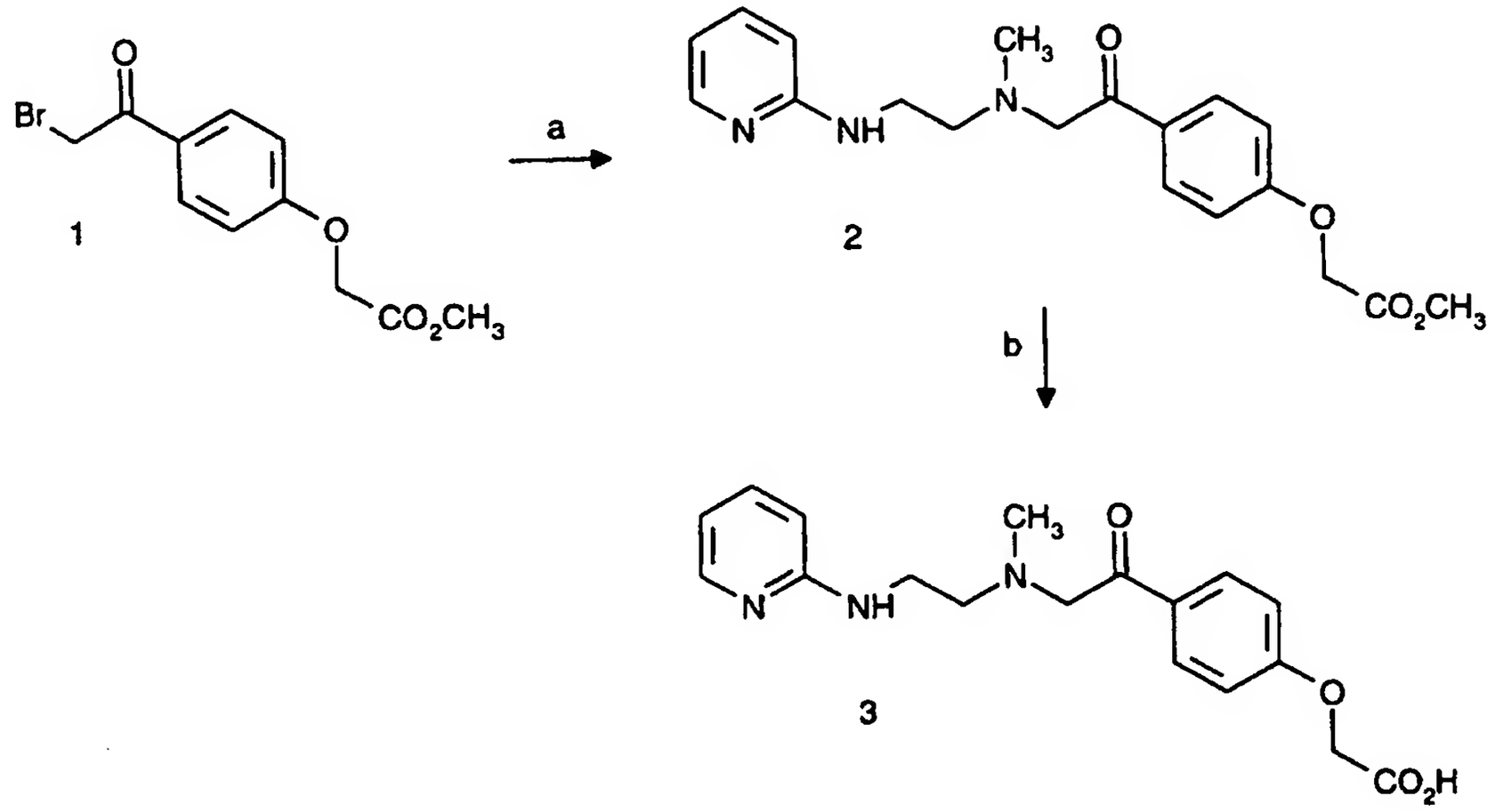



a) N-(2-pyridinyl)ethylenediamine, $Ph_2POCl$, $Et_3N$, DMAP, THF; b) NaH, $BrCH_2CO_2CH_3$, DMF; c) KOtBu, $CH_3I$, DMF; e) LiOH, $H_2O$, THF.

Following the procedures of Linz, *et al.*, EP 0567968, except substituting N-(2-pyridinyl)ethylenediamine for 4-cyanoaniline, gives **Q-5**.

Scheme R describes a method of preparing exemplary fibrinogen receptor templates described in Wayne, *et al.*, WO 94/22834.

**Scheme R**




a) N-methyl-N'-(2-pyridinyl)ethylenediamine, $CH_3CN$; b) 1N NaOH, $CH_3OH$

Following the procedures of Wayne, *et al.*, WO 94/22834, Example 1-2, except substituting N-methyl-N'-(2-pyridinyl)ethylenediamine for 1-(4-pyridyl)piperazine gives **R-3**.

Scheme S describes a method of preparing exemplary fibrinogen receptor templates described in Wayne, *et al.*, WO 94/22834.

**Scheme S**